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VITAMIN STATUS OF THE POPULATION OF THE WEST COAST OF NEWFOUNDLAND WITH EMPHASIS ON VITAMIN C *

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THE isolation and synthesis of many of the vitamins have given a tremendous impetus to the study of nutrition throughout the world. Investigations have been conducted in various countries in widely separated areas of the globe to determine the actual vitamin status of the population and to establish, if possible, its relationship to health and disease in these areas.[1]

During the past year a survey has been carried out to determine the effects of prolonged deprivation of normal dietary intake of vitamins upon members of the population of the West Coast of Newfoundland.

The purpose of this paper is twofold: first, to present the background against which this survey was carried out; and second, to present in summary certain information obtained during this study.

The district covered in this investigation is that served medically by the Bonne Bay Cottage Hospital located at Norris Point, Newfoundland. The population comprises some 600 families with an average of about six persons per family, scattered over a coastal area of some 60 miles' extent, including Bonne Bay. Because of the curtailed medical assistance on this coast during the winter of 1941–1942, patients were seen from districts further down the coast in more isolated areas. The population is grouped in small communities ranging from 15 to 800 people. There are 23 communities in all. Nearly all the families live in houses situated from a few feet to a few hundred yards from the sea, except in winter when moderately large groups

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move inland to be near the logging camps. Occupational opportunities are usually seasonal and are connected either with some branch of the fishing industry, i.e., lobster, cod, salmon or herring fishing, or of the lumber industry, with one of the large pulp and paper companies, or with operating small portable saw mills. Every family has its own garden where the main crops are potatoes, cabbage and turnips, with a small amount of grass land for winter fodder. Nearly every family has some sheep, a great many have a horse, but relatively few have cows or goats, with the result that the milk supply is limited. Absence of transportation, refrigeration and storage facilities, together with restricted educational opportunities which are found invariably in regions of low population density, play a part in the dietary problems of this district. During the summer months, a motor road connecting with the railroad supplements the coastal boats as a means of transportation. After the harbors and bays are frozen and the road closed to motor traffic, transportation is limited to dog teams. If the ice is in good condition, travel is easier. Transportation is most difficult during the periods of the fall rains and the spring thaw. Although natural ice is available for refrigeration a part of the year, much meat may be lost by sudden change in temperature, and at present there is little general provision to guard against such loss.

The educational opportunities for this region have been limited in past years, many communities to the north having no schools or inadequate institutions. In the fall of 1942, however, compulsory education was adopted and the educational standards will be improved gradually.

The diet available to this district is listed in table 1. Certain foodstuffs may be obtained at all times and form the main source of food supply. Other foodstuffs are available for short periods depending upon the growing, fishing and hunting seasons. The fact that vegetables and berries are listed as available does not mean necessarily that these are utilized, for many persons restrict their diets through ignorance, prejudice and faulty preparation of foods. Dairy products are extremely difficult to obtain and even where cattle are kept there is apt to be a traditional distaste for milk which is used only sparingly in tea. Limited supplies of citrus fruits are available during the summer months and for intermittent periods during the winter. These are considered usually as tasty adjuncts but rarely as a necessary component of the diet. There are a few families whose financial and educational status is above the level of the rest of the population. These, by virtue of their information, can use the material at hand to better advantage. They too, however, are subject to the restrictions imposed upon them by their geographical position. The foodstuffs available to the men in the lumber camps during the winter months, and to the fishermen who go down to Labrador is even more restricted than that available to the general population (see table 1). Their diet is high in carbohydrates and fats, and moderately high in proteins, but very deficient in the protective foodstuffs.

TABLE I

Foodstuffs Available to the Population of the Bonne Bay District

Period Available	Fish	Meat	Berries Vegetables	Dairy Products Substitutes Eggs	Cereals	Fruits	Miscellaneous
Year round	Salt cod*† Herring*†	Salt beef*† Salt pork*† Tinned meats Bologna	Potatoes*† Turnip (Swede) Beans (dried)† Onions†	Margarine†	Oatmeal*† Cornmeal*†	Canned peaches Canned pineapple Canned pears Dried prunes† Dried apricots*† Dried apples*† Dried dates	Molasses*† Sugar*† White flour*† Tea*†
Seasonal	Lobster* Salmon* Trout* Herring*	Spring: Mutton† Beef† Seal* Winter: Beef† Rabbit† Moose Birds*	Carrots*† Turnips*† Cabbage*† (March latest) Turnip greens Parsnips† Beets Dandelions Partridge berries	Eggs†		Raspberries Bakeapple berries* Blueberries Damsons Apples†	
Rare		Bacon*†	Lettuce	Milk except in tea (tinned)*† Butter Cheese† Eggs		Citrus fruit Bananas	Nuts Whole wheat bread

* Foodstuffs available to fishermen (Labrador). † Foodstuffs available to woodsmen.

METHODS

The patients studied in this survey included those admitted to the ward service of the Bonne Bay Cottage Hospital, those seen in the antenatal clinic and service, and as many patients in the outpatient department as facilities permitted. Complete histories were taken to determine the types of food ingested, though no attempt was made to determine caloric intake. Medical histories were taken in an attempt to evaluate the symptoms which might be traced to dietary deficiencies. Blood vitamin C determinations were carried out on nonfasting specimens following the technic of Farmer and Abt.[2] All readings were done in triplicate. Five-hour saturation tests were done where indicated.[3] Capillary fragility tests [4] and hemoglobin estimations were carried out. Ether extractions of urines to determine the presence of urosein were also performed.[5]

TABLE II

Vitamin C Blood Levels in 321 Untreated Patients (454 Determinations)

Blood Vitamin C Mg./100 c.c. Plasma	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Average %
Saturated 1.0 –2.0					1			4	8	21	4	5	9.5
Satisfactory 0.7 –1.0	1	1					1	3	7	7	5	5	6.6
Suboptimal 0.5 –0.7	8	2	1		2	2		3	5	12	13	10	12.8
Vitamin C deficiency													
A. 0.3 –0.5	17	16	9	5	11	7	3	10	4	6	6	11	23.1
B. 0.15–0.3	14	13	18	19	23	16	7	13	2	1	4	2	29.1
C. 0.00–0.15	3	9	6	18	11	20	4	10	2	3		3	19.6
No. of determinations	43	41	34	42	48	45	15	43	25	50	32	36	454
Average vitamin C mg./100 c.c.	.34	.29	.25	.18	.24	.20	.25	.38	.75	.82	.60	.57	.41

RESULTS

In table 2 a summary of vitamin C studies on all patients is presented. The blood vitamin C levels can be correlated with the available vitamin C in foodstuffs for the various months. As the supplies of fresh foods decreased, the blood levels were reduced. The lowest level (0.18 mg. per cent) was reached in April. The average for the entire group for the year was 0.41 mg. per cent. Patients in the saturated levels during October were found to be in the deficient groups when rechecked in the early Spring. The most consistent clinical signs upon examination of the entire group of patients were dental caries, gingivitis, and hyperkeratosis.

The distribution of blood vitamin C levels among the antenatal patients seen during this survey is indicated in table 3. . This table reveals more clearly the months in which the diet is severely restricted, as there are no readings in the normal or satisfactory levels during the first seven months of the year.

In table 4 the same data presented in table 3 are rearranged according to the month of gestation. Although there are reports in the literature indicating that there is a gradual decrease in blood vitamin C level as the period of gestation progresses, it is difficult to interpret our figures in this light, as the blood levels in most instances seemed to be dependent upon the month of the year and the vitamin C available at that time rather than on the month of pregnancy.

TABLE III

Vitamin C Blood Levels in 58 Antenatal Patients (121 Determinations)
(First visit and untreated revisits arranged according to calendar months)

Blood Vitamin C Mg./100 c.c. Plasma	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Average %
Saturated 1.0 –2.0								1	3	6	3		10.8
Satisfactory 0.7 –1.0									1	4	4	4	10.8
Suboptimal 0.5 –0.7	3	2				2			1		4	5	14.1
Vitamin C deficiency													
A. 0.3 –0.5	7	4	3	3	6	1		4		1	2	2	27.3
B. 0.15–0.3	5	3	5	3	3	2	1	3					20.7
C. 0.00–0.15	1	3	3	4	2	3		3				1	16.5
No. of determinations	16	12	11	10	11	8	1	11	5	11	13	12	121
Average vitamin C mg./100 c.c.	.34	.30	.22	.20	.27	.28	.19	.36	1.14	.91	.76	.58	.46

TABLE IV

Vitamin C Blood Levels in 58 Antenatal Patients (121 Determinations)
(First visit and untreated revisits arranged according to month of gestation)

Blood Vitamin C Mg./100 c.c. Plasma	Months								
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Saturated 1.0 –2.0		1	2	2				5	3
Satisfactory 0.7 –1.0		1	1	3	1	1	3	1	2
Suboptimal 0.5 –0.7	1	1		2	4	2	3	2	3
Vitamin C deficiency									
A. 0.3 –0.5			3	2	5	3	4	5	9
B. 0.15–0.3		1	3	5	1	2	5	4	4
C. 0.00–0.15	1			4	1	2	6	1	6
No. of determinations	2	4	9	18	12	10	21	18	27
Average vitamin C mg./100 c.c.	.31	.84	.55	.46	.43	.37	.34	.58	.43

In seven instances we were able to obtain samples of cord blood at time of delivery and carried out vitamin C determinations on these specimens. The vitamin C levels in the cord blood plasma were higher than in the maternal blood in each instance even when the maternal blood level was extremely low. Our studies demonstrated that whereas there is a selective filtration of vitamin C by the placenta, there is a possibility of latent scurvy at birth if the mother has been on a prolonged diet deficient in that vitamin. A more detailed report of this work has been published elsewhere.[6]

The studies done on woodsmen and fishermen are presented in table 5. This group of men lives on a diet very low in vitamin C and the effects of this are obvious upon examination of the data presented. The blood levels of the men in this group fell below the satisfactory levels except in one instance. This man was acting as assistant to the camp cook and his diet may well have been above the average. In most instances these men came into the clinic with minor complaints, chiefly dental caries.

TABLE V

Vitamin C Blood Levels in 33 Woodsmen and Labrador Fishermen

Blood Vitamin C Mg./100 c.c. Plasma	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Average
Saturated 1.0 –2.0													
Satisfactory 0.7 –1.0	1												
Suboptimal 0.5 –0.7	2								1	1	1	1	
Vitamin C deficiency													
A. 0.3 –0.5	2	2								1	2	2	
B. 0.15–0.3	3	2	3	3	2	1	(oranges)						
C. 0.00–0.15					1	1		1					
Average vitamin C mg./100 c.c.	.42	.33	.24	.22	.15	.16	—	.07	.63	.53	.44	.41	.30

A comparison of the blood vitamin C levels of the three groups represented in tables 2, 3 and 5 is demonstrated in figure 1.

The hemoglobin levels of the three groups are shown in figure 2. Although there were wide individual variations, the average for the various groups does not differ markedly from those reported for other regions of the world.[7]

TABLE VI

Results of 227 Capillary Fragility Tests in Relation to Degree of Saturation

Blood Vitamin C Mg. %	Normal 0–10*	Borderline 11–20*	Pathological above 20*
Saturated 1.0 –2.0	17 (49%)	6 (17%)	12 (34%)
Satisfactory 0.7 –1.0	9 (64%)	2 (14%)	3 (21%)
Suboptimal 0.5 –0.7	13 (52%)	6 (24%)	6 (24%)
Vitamin C deficiency			
A. 0.3 –0.5	34 (68%)	7 (14%)	9 (18%)
B. 0.15–0.3	31 (55%)	7 (14%)	18 (33%)
C. 0.00–0.15	21 (58%)	4 (11%)	11 (31%)

* Number of petechiae.

Table 6 reveals a high percentage of patients with normal capillary fragility in vitamin C deficiency states. This finding reëmphasizes the warning made previously by one of us [8] of the danger of over-interpreting the results of this test and of relying upon it to the exclusion of chemical studies to establish the vitamin C status of the patient. Many of the patients had severe secondary anemia. Normal capillary fragility has been reported with anemic states in the presence of vitamin C deficiency.[8]

Since laboratory facilities were not available for studies of the members of the vitamin B complex, and since to date the detection of deficiencies in this group is dependent upon clinical observation, we questioned and examined 284 patients to determine whether their symptoms might be related

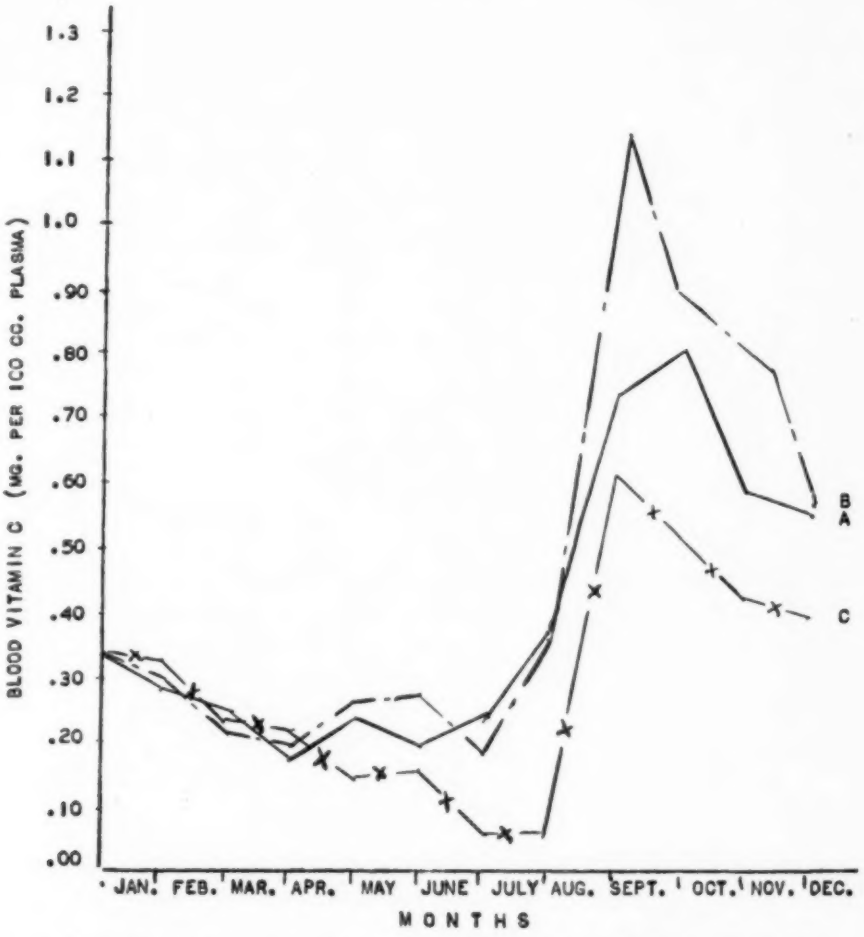

FIG. 1. Comparison of average monthly determinations of blood vitamin C.
A. ———— Average monthly blood vitamin C, 454 determinations, 321 patients, routine
B. — — — — Average monthly blood vitamin C, 121 determinations, 58 antenatal patients
C. —x—x— Average monthly blood vitamin C, 33 determinations, 33 woodsmen and fishermen
All determinations first visits and untreated revisits

to deficiencies in the B group. As reported in table 7, the following signs and symptoms were among the most frequently noticed. Those related to the gastrointestinal system were the most common including constipation, anorexia, flatulence and indigestion. Constipation was usually of long duration and periods of from three to eight or more days between stools

were commonly noted. Neurological signs were noted including absence or diminution of reflexes, foot drop of beriberi, numbness and tingling of extremities, and areas of disturbed sensation especially over the lower extremities including the soles of the feet. Muscular weakness and cramps in the legs were also observed. These were not primarily on a vascular basis

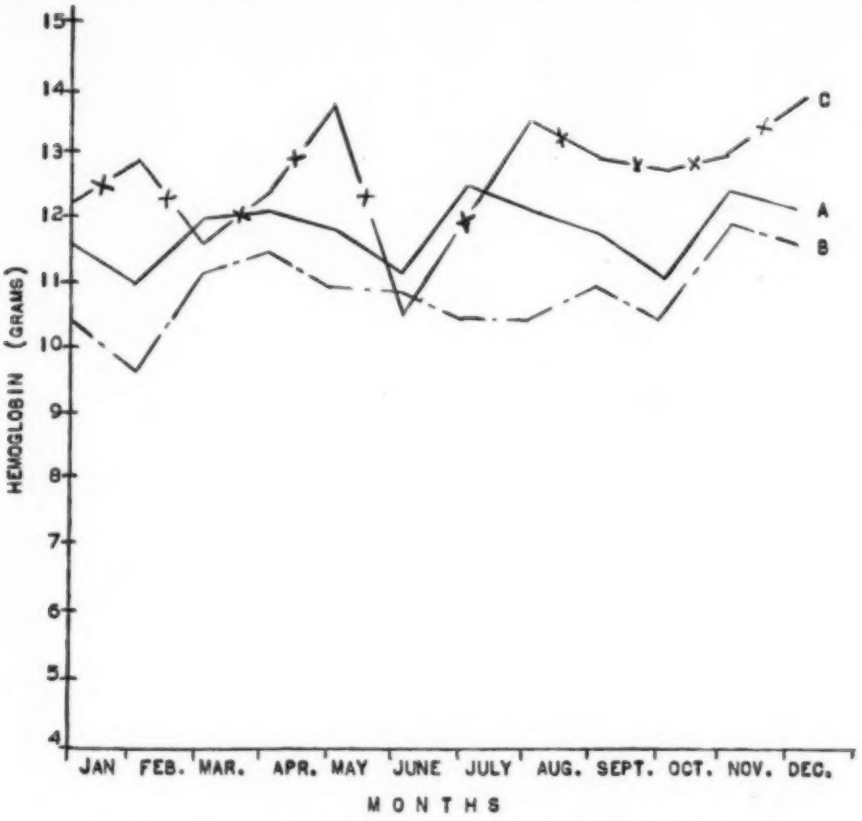

FIG. 2. Comparison of average monthly hemoglobin determinations.

A. ———— Average monthly hemoglobin determinations entire group 296, yearly average 11.9

B. – – – – – Average monthly hemoglobin determinations 58 antenatal patients, yearly average 10.8

C. —x—x— Average monthly hemoglobin determinations 33 woodsmen and fishermen, yearly average 12.6

and improved upon adequate amounts of thiamin chloride. Visual disturbances which appeared to be unrelated or caused only in part by vitamin A deficiency were observed. These were marked by increased lacrimation, itching and burning of the eyes, photophobia and increased vascularization of the sclera. We had the opportunity of observing four cases of acute snowblindness following exposure which seemed to be on a vitamin basis. These patients were seen during the early spring months (April and May) and suggest that the deficient diet is to be considered as a joint causative

TABLE VII

Summary of Signs and Symptoms Usually Related to Vitamin B Complex Deficiency and Seemingly Unexplained on Any Other Basis in 284 Patients

Ocular		Gastrointestinal		Cardiac		Neurological		Constitutional	
Photophobia	19	Cheilosis	49	Undue awareness of heart	8	Numbness and tingling	28	Loss of weight	6
Congested sclera, increased lacrimation	28	Tongue and mouth	48	Shortness of breath	72	Absent or diminished reflexes	5	Fatigue	70
Snowblindness	4	G.I. distress	41			Diminished areas of sensation	9	Nervousness	16
		Epigastric and anorexia	52			Tenderness along nerve courses	2		
		Flatulence	5			Burning of soles of feet	18		
		Constipation	111			Neuritis	5		
						Leg cramps	13		

Patients showing vitamin B deficiency symptoms	233
Patients showing no vitamin B deficiency symptoms	51

agent along with exposure to intense glare. All four patients responded to massive doses of riboflavin. One patient had a corneal ulcer at the time of admission which was healed completely following eight days of therapy. Certain cardiac disturbances disappeared upon adequate treatment with thiamin chloride and reappeared when therapy was discontinued or was inadequate. Organic cardiac changes were unimproved following therapy.

Involvement of the tongue and lips was observed in 48 patients and included cheilosis, swelling, soreness, denuding and discoloration of the tongue. Nasolabial scaliness was also observed.

No classical pictures of pellagra were seen during this survey, although in several instances histories of disturbances of sensation resembled those found in this condition. In one instance severe psychic aberration was improved following nicotinic acid therapy.

The total number of patients exhibiting signs and symptoms which are usually related to the vitamin B complex deficiency was 233. This number represents 72 per cent of the entire group included in the survey and 82 per cent of the number questioned and examined.

DISCUSSION

The blood vitamin C levels for the population of the district fell within normal ranges for only two months of the year and were dependent upon the supply of foodstuffs containing that substance.

As has been observed and reported in the literature, changes in the structure of the teeth occur following prolonged self-deprivation of vitamin C.[9] As the majority of the population are on diets low or completely lacking in vitamin C for long periods of each year, it would seem that this factor should be considered to be contributing to the widespread presence of dental caries.

The relation of vitamin deficiency to the onset of tuberculosis has not been fully clarified, but it is of interest to note the possible relationship between the low vitamin C levels and the high incidence of tuberculosis in this region. The previously mentioned low average intake of vitamin C makes it evident in this study that deficiencies in this vitamin cannot be entirely attributed to the increased demand for vitamin C due to the infectious process of the disease itself.

In an earlier report by us it was pointed out that the incidence of infantile scurvy was probably higher than formerly believed, and this should be kept in mind when studying the factors contributing to the high infant mortality for this whole country.[6]

During a portion of 1940, Dr. J. M. Olds of Twillingate carried out some studies on the East Coast of Newfoundland on 100 patients admitted to the hospital in that community. Although no mention is made in his report to the Newfoundland Medical Association [10] of the months during which these studies were carried out, his figures coincide with ours and confirm the belief that similar conditions exist in other remote sections of Newfoundland.

Probably the chief source of vitamin C in the average diet of these people is the Irish or white potato. This vegetable is considered by some authorities to be a good source of vitamin C as is the Swede turnip which is also widely used for many months. Even though it is recognized that much vitamin C is lost through storage and faulty preparation, these two vegetables are the chief source of vitamin C during the long winter months. It is clear from the figures presented that they do not provide an adequate source of vitamin C.

The widespread use of refined white flour, the preference for salt fish and salt meats, the lack of adequate amounts of leafy green vegetables and milk in the diet, all contribute to the numerous manifestations of deficiencies in the B complex. The relationship of fat metabolism to the utilization of thiamin chloride is of great importance and the average high fat intake may be a factor explaining the relatively low incidence of advanced beriberi encountered during this survey.

The deficiencies observed in this district were, in most instances, multiple in nature as would be expected in a region where the dietary possibilities are restricted.

Summary

A survey of the vitamin status of the population of the West Coast of Newfoundland is reported. As this section has been settled during the last 75 to 80 years, approximately three or four generations have been subjected

to similar conditions. The people in this area are isolated and on a diet depleted in protective food factors for a large part of every year. It is felt that any information gained by the study of groups on depleted diets might be of value in the handling of other malnourished populations during and after this war.

Clinical and chemical studies on the vitamin C status of 321 unselected hospital and clinic patients have been analyzed. Vitamin C blood levels were followed in 58 antenatal patients as well as in 33 woodsmen and fishermen. Each of these groups shows a marked seasonal variation which is parallel to the available vitamin C sources in the diet.

It has been shown that there is a selective filtration of vitamin C by the placenta.

The capillary fragility test and hemoglobin levels of the three groups are presented.

Vitamin B deficiency was determined by clinical history and physical examination. Two hundred and 84 patients were studied in this regard and evidence of vitamin B deficiency (at least of one of its components) was noted in 233 patients (82 per cent of those studied). As in most individuals on depleted diets, the evidence demonstrated multiple rather than single vitamin deficiencies.

Since the completion of this survey, a campaign is being planned jointly by the Department of Public Health and Welfare of the Newfoundland Government and the Nutrition Council of the Newfoundland Medical Association to correct the situation revealed by this work.

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MENINGOCOCCIC INFECTIONS; REPORT OF 43 CASES OF MENINGOCOCCIC MENINGITIS AND 8 CASES OF MENINGOCOCCEMIA *

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Recent reports indicate that there has been a marked increase in the incidence of cerebrospinal fever in Great Britain since the outbreak of the present war and similar increases have been noted more recently in Canada and the United States.[1, 2, 3, 4, 5] These reports have also indicated that there has been a striking reduction in the case fatality rate in this disease as a result of the use of sulfonamide drugs. The literature concerning the present status of the diagnosis and treatment of meningococcic meningitis has been summarized recently by Dingle and Finland.[6] The present report deals with 51 cases of meningococcic infections admitted to the Boston City Hospital in the two-year period beginning September 1, 1940. It is the purpose of this paper to emphasize certain of the less commonly recognized features of the clinical course, the laboratory findings and the therapy of these infections.

Included among the 51 cases were 43 with meningitis and eight cases of meningococcemia without clinical evidence of meningitis. These two groups of cases will be considered separately.

Meningococcic Meningitis

Of the 43 cases of meningococcic meningitis, 14 were admitted to the hospital between September 1940 and August 1941 and 29 were admitted during the following year. There were 23 males and 20 females. They varied in age from two months to 65 years: 15 were under 10, 13 were between 10 and 29, and 15 were 30 or over. Certain of the relevant data in these cases are shown in table 1.

Predisposing Factors. Except in one patient who had a head injury prior to admission, alcoholism was probably the only predisposing factor which contributed to the severity of the illness in these cases. Three patients were moderate and three were severe chronic alcoholics. Two of the latter died

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Dr. Thomas was a Fellow of the Frederick Tilney Memorial Fund.

TABLE 1

TABLE I

Summary of Pertinent Data in 43 Cases of Meningococcic Meningitis (Boston City Hospital; September 1940 through August 1942)

Case No.	Sex	Age, yrs.	Duration at Entry	Severity	Bacteriology on Admission			Chemotherapy							Duration after Chemotherapy					Comments (Autopsy Findings, Complications, Antiserum Therapy, etc.)
					Blood Cultures	Cerebrospinal Fluid		Drug	Route	Duration	Total, grams	Blood Level, mg./100 ml. (Free)			Definite Clinical Improvement, hours	Fully Rational, days	Afebrile	Cerebrospinal Fluid Culture		
						Cultures	Smear					After 12 hours	After 24 hours	Average First Week				Last Positive §	First Negative	
1	M	64	24 h.	++++	M I	M I	+	SD	s.c.	6 h.	5	0.5	–	–	–	–	Died	–	–	Severe alcoholism.
2	F	58	12 h.	++++	–	0	+	SD	s.c.	13 h.	10	8.6	–	–	–	–	Died	–	–	Autopsy: Diffuse encephalitis, slight; capillary thrombi in brain; cerebellar pressure cone; adrenal hemorrhages (microscopic); purulent meningitis.
3	M	15	2 d.	++++	0	M I	+	SD	p.o.	6 h.	7	3.8	–	–	–	–	Died	–	–	Autopsy: Purulent meningitis; cerebral edema, marked; cerebellar pressure cone.
4	M	64	24 h.	++++	M I	M I	+	SD	i.v., s.c.	46 h.	10	18.8	–	–	–	–	Died	19 h.	43 h.	Autopsy: Purulent meningitis; bronchopneumonia, left lower lobe; C.N.S. syphilis.
5	M	39	2 d.	++++	0	M I	+	SD	i.v., s.c., p.o.	50 h.	23	17.0	–	–	–	–	Died	24 h.	48 h.	Severe alcoholism. Antimeningococcus rabbit serum, 60 c.c. i.v. given 26 hours after SD. Autopsy: Purulent meningitis.
6	F	2½	12 h.	++++	M	0	+	ST, SP	p.o.	26 h.	11	–	–	–	–	–	Died	–	–	Antimeningococcus rabbit serum, 15 c.c. given i.v. 3 hours before death.
7	M	47	?	++++	M II	M II	+	SD	p.o.	12 h.	7	0.5	–	–	–	–	Died	–	–	Autopsy: Purulent meningitis; bronchopneumonia; acute pericarditis.
8	F	5	12 h.	++++	M I	–	–	SD	p.o.	2 h.	1	–	–	–	–	–	Died	–	–	Clinically a typical case of Waterhouse-Friderichsen syndrome; no autopsy.
9	F	35	24 h.	++++	M IIα	M IIα	+	SD	i.v.	6 h.	5	–	–	–	–	–	Died	–	–	Autopsy: Minimal meningitis; large bilateral adrenal hemorrhages.
10	M	57	24 h.	++++	M I	M I	+	SD	i.v., p.o.	10 d.	67	11.0	9.3	9.1	12	1	5 d.	0	18 h.	Alcoholism, moderate. Delayed mental depression.
11	M	28	5 d.	++++	M I	M I	+	SD	i.v., p.o.	11 d.	73	–	1.4	3.9	72	6	7 d.	0	1 d.	Head injury (? cerebral laceration); paralysis right lateral rectus muscle.
12	M	21	10 d.	++++	M I	M I	+	SD	i.v., p.o.	9 d.	55	7.4	7.5	7.4	24	4	6 d.	11 h.	24 h.	Alcoholism, moderate.
13	M	16	2 d.	++++	M I	M I	+	SD	i.v., p.o.	9 d.	53	4.8	–	8.6	12	2	3 d.	0	2 d.	
14	M	15	2 d.	++++	0	M I	–	SD	i.v., s.c., p.o.	9 d.	49	–	–	9.2	12	3	6 d.	0	24 h.	
15	F	41	24 h.	++++	0	0	+	SD	i.v., p.o.	9 d.	73	–	16.3	11.0	24	4	6 d.	0	–	Thrombophlebitis, left leg.
16	M	34	24 h.	++++	0	M	+	ST, SD	i.v., p.o.	13 d.	107	–	8.3	10.6	18	6	7 d.	0	18 h.	Alcoholism, moderate; ill health, 1 year.
17	F	56	2 d.	++++	M II	M II	–	ST, SP	p.o.	13 d.	72	–	–	8.3	24	–	24 h.*	0	19 h.	Alcoholism, severe.
18	M	20	2 d.	++++	0	M II	+	SP	i.v., p.o.	11 d.	70	–	2.7	2.1	28	3	3 d.	8 h.	17 h.	Received 30 c.c. of 0.2% solution SP intrathecally.
19	F	58	24 h.	++++	M I	M I	+	SD	s.c., p.o.	15 d.	89	–	18.4	17.7	42	–	7 d.	10 h.	22 h.	Antimeningococcus, Type I, rabbit serum 60 c.c. i.v., 14 hours after SD.

TABLE I—*Continued*

Case No.	Sex	Age, yrs.	Duration at Entry	Severity	Bacteriology on Admission			Chemotherapy							Duration after Chemotherapy					Comments (Autopsy Findings, Complications, Antiserum Therapy, etc.)
					Blood Cultures	Cerebrospinal Fluid		Drug	Route	Duration	Total, grams	Blood Level, mg./100 ml. (Free)			Definite Clinical Improvement, hours	Fully Rational, days	Afebrile	Cerebrospinal Fluid Culture		
						Cultures	Smear					After 12 hours	After 24 hours	Average First Week				Last Positive §	First Negative	
20	F	18	2 d.	+++	M I	M I	+	SD	i.v., p.o.	8 d.	47	—	11.4	8.7	'24	1	6 d.	0	2 d.	Paresis right lateral rectus muscle.
21	M	2	3 d.	+++	X	M I	+	SA, SD	p.o.	15 d.	50	—	—	5.0	12	—	6 d.	0	4 d.	
22	M	3½	24 h.	+++	0	M II	—	SP, SD	p.o.	24 d.	60	—	20.5	—	24	1	10 d.	1 d.	3 d.	Vomited SP for first 3 days.
23	M	5	4 d.	+++	0	0	0	SD	p.o.	11 d.	24	—	—	—	8	1	8 h.	0	—	M I from nasopharynx; bilateral total deafness; slight ataxia.
24	F	8/12	24 h.	+++	—	M	+	SA	p.o.	14 d.	37	—	9.7	12.5	?	—	14 d.*	0	2 d.	Rickets, severe.
25	M	20	3 d.	+++	0	M	+	SD	p.o.	7 d.	39	—	5.7	6.7	18	1	32 h.	0	10 d.	Meningitis (M II) 6 months previously (Case 18).
26	M	2½	12 h.	+++	M	M	—	SP, SA	p.o.	11 d.	30	—	—	—	?	—	8 d.	0	1 d.	
27	F	31	24 h.	++	M I	M I	+	SD	i.v., p.o.	20 d.	71	—	23.0	20.2	12		12 h.	0	18 h.	Pneumonitis and interlobar fluid on 11th day.
28	M	5	3 d.	++	—	M I	0	SP, SA, SD	p.o.	10 d.	30	—	—	—	18		4 d.	0	3 d.	Vomited SP first day.
29	M	11/12	2 d.	++	—	M I	+	SD	p.o.	35 d.	37	—	—	17.0	?		33 d.	0	1 d.	Antimeningococcus horse serum, 5 c.c. i.v. and 5 c.c. intrathecally.
30	F	2	24 h.	++	—	M II	—	SP	p.o.	11 d.	14	—	—	—	24		5 d.	0	1 d.	
31	M	65	5 d.	++	0	M II	+	SD	p.o.	16 d.	90	—	—	4.2	24		7 d.	0	1 d.	Serological syphilis; right cerebral thrombosis; chronic heart disease.
32	F	12	24 h.	++	—	M	+	SA	p.o.	4 d.	33	—	—	—	24		24 h.	0	1 d.	
33	F	1½	24 h.	+	—	M I	—	SD	p.o.	15 d.	29	—	—	—	24		11 d.*	0	—	
34	F	2/12	3 d.	+	X	M IIα	+	SD	s.c., p.o.	19 d.	31	—	15.6	12.7	24		5 d.*	1 d.	3 d.	
35	F	30	2 d.	+	0	M IIα	+	SD	s.c., p.o.	14 d.	83	—	17.0	10.5	24		6 d.	0	24 h.	
36	M	2	24 h.	+	0	M I	+	SD	s.c., p.o.	16 d.	31	—	21.4	12.9	24		17 d.*	17 h.	2 d.	Slight ataxia.
37	F	23	10 d.	+	0	0	+	SD	i.v., p.o.	10 d.	59	—	—	9.1	20		24 h.	0	—	
38	F	24	4 d.	+	—	M	+	SD	p.o.	5 d.	27	—	2.7	7.9	24		36 h.	0	3 d.	8 months pregnancy; full term normal delivery later.
39	F	3	2 d.	+	0	M	+	SP	p.o.	12 d.	28	—	—	—	?		5 d.*	0	2 d.	
40	F	24	3 d.	+	0	0	0	SD	i.v., p.o.	6 d.	39	—	8.4	7.0	12		12 h.	—	—	4 months pregnancy; full term normal delivery later; typical clinical course with rash.
41	M	13	6 d.	+	0	M I	+	SD	p.o.	6 d.	40	—	10.0	14.6	12		3 d.	0	5 d.	
42	M	54	2 d.	+	M I	M I	+	SD	p.o.	11 d.	70	—	8.1	7.8	18		3 d.	0	12 d.	
43	F	4	?	+	—	—	+	SP	p.o.	12 d.	33	—	—	—	20		4 d.*	—	—	

Abbreviations and explanations: Sex: M = male; F = female. *Duration:* h. = hours; d. = days. *Severity:* ++++ = severe (comatose or moribund on admission); +++ = acutely ill (semicomatose or delirious); ++ = moderately ill (rational but in acute distress); + = mild (rational, slight distress). *Bacteriology:* + = positive for gram-negative diplococci; M = meningococcus type not determined; I, II, IIα represent Group designations; X = contaminant. *Chemotherapy:* SA = sulfanilamide; SP = sulfapyridine; ST = sulfathiazole; SD = sulfadiazine; i.v. = intravenous; s.c. = subcutaneous; p.o. = oral or through a stomach tube. — = not done or information not available. * = drug fever. § In this column 0 = no positive cultures obtained after admission.

and the others were all severely ill. This is of interest, by analogy, in view of the loss of local resistance to Type I pneumococcic infection demonstrable in rabbits which are kept stuporous with alcohol.[7] In addition there were two patients with chronic heart disease, one with central nervous system syphilis, and two who had been in ill health for a year prior to this illness. Two of the women were pregnant, one in the fourth month and the other in the eighth. In none of the patients was any history of possible contact with other similar cases elicited.*

Upper Respiratory Tract Infections. Almost all of the patients with meningitis had evidence of an acute upper respiratory tract infection shortly before, or at the time of entry to the hospital. In 31 of the cases the admission physical examination revealed an active or subsiding pharyngitis. Five other patients gave a history of an upper respiratory tract infection which had subsided by the time of admission and data are lacking in six of the remaining seven cases.

Clinical Features

Onset and Early Symptoms. The occurrence of the most frequent symptoms and signs is shown in table 2. The large majority of the patients presented the classical features of meningitis. After an upper respiratory

Table II

Clinical Finding	Per Cent of Cases
Upper respiratory tract infection	97
Rash	88
Headache*	100
Vomiting	100
Stiff neck	95
Positive Kernig sign	97

* In patients 5 years of age or older.

tract infection, usually a simple pharyngitis, of several days' duration, the disease was ushered in by symptoms commonly associated with bacterial invasion of the blood stream or the meninges. These included a sudden onset of increasing malaise soon followed by headache and vomiting. In addition there were single or repeated chills, rash, arthralgia, myalgia and stiff neck. Each patient presented several of these features but all of them were seldom present in the same patient. The duration of illness before entry varied from 12 hours to 10 days. Two-thirds of the patients were admitted within two days of the onset and four-fifths of them were admitted in the first three days.

* The only instance of contact infection observed during this period was in an interne not included in this series. A patient with Group I meningococcic meningitis coughed violently into the interne's face while he was passing a stomach tube. Three days later the interne had a slight conjunctivitis which subsequently became purulent. After two more days he developed a sore throat. Group I meningococci were obtained from cultures of his eye and of his nasopharynx. He was treated with sulfathiazole and improved promptly and completely. The interne remained on duty throughout this episode and had no discomfort at any time.

Severity. The cases varied considerably in the severity of the illness which they presented at the time of admission to the hospital. Sixty per cent of the cases were either comatose, stuporous or delirious at the time of entry, while the remaining 40 per cent of the cases were quite rational. The illness of the latter cases was considered to be moderate or mild. Some of the milder cases had little or no discomfort and in them the diagnosis was not always made or suspected when they were first seen in the hospital.

Rash. A petechial or purpuric rash was present in most of the cases. In five instances the patient gave a history of such a rash, but it was no longer present at the time of admission. One patient, who entered on the tenth day of his illness, told of a rash at the time of onset which had cleared entirely only to recur five days later.

Stiff Neck. This sign was present in all but two of the cases. One of these was a case with the clinical characteristics of the Waterhouse-Friderichsen syndrome and autopsy revealed bilateral adrenal hemorrhages and a minimal amount of meningitis. In the other case, however, there was extensive exudate over the cerebral cortex and especially at the base of the brain. *A positive Kernig sign,* on the other hand, could be elicited in only 57 per cent of the cases.

Pulmonary Involvement. Abnormal physical signs in the lungs were surprisingly frequent at the time of admission. Râles and varying degrees of changes in the breath sounds were made out in 16 patients, and two others had rusty sputum without abnormal signs in the lungs. Roentgenograms were taken in seven cases and confirmed the findings of lobar or bronchopneumonia in five of them. None of these 16 individuals had any evidence of myocardial insufficiency.

Fever. The temperature on admission varied from 96° to 105° F.; it was 100° or below in 10 patients and 99° or less in five of them. Two patients had subnormal temperatures (96°): one of them had the Waterhouse-Friderichsen syndrome and died a few hours after admission, and the other's temperature remained subnormal until after 48 hours of therapy when it rose to 100° and stayed at this level for the next three days.

The *pulse rate* on admission varied from 70 to 160 per minute. There was a relative bradycardia (rate of 70 to 80) on admission in eight patients in whom the temperature was between 100 to 103°. This disparity between temperature and pulse rate existed for several hours and in some cases as long as 24 hours. The low pulse rates were not apparently related to the severity of the illness; four of the patients were considered to be severely ill and the other four had only a moderate or mild illness.

The accepted explanation of bradycardia in meningitis is that it is due to increased intracranial pressure. This undoubtedly plays an important rôle in some cases, but there are probably other factors as well. The initial pressure of the cerebrospinal fluid was 300 mm. of water or greater in seven of the eight patients having a pulse rate of 80 or lower, and it was 100 mm. in the eighth case. There were 10 other patients, however, in whom pres-

sures of 300 to 500 mm. in the cerebrospinal fluid were not associated with bradycardia.

Blood Findings. The white blood cell counts were elevated on admission in all the cases. They varied between 12,000 and 42,000 per cubic millimeter of blood, the average being 21,000. Mild anemia was present in some of the young children.

Results of First Lumbar Puncture

The cerebrospinal fluid findings at the time of the first lumbar puncture showed the abnormalities which are usually expected in cases of acute bacterial meningitis.[8] There were, however, certain discrepancies in some of the cases and these are worth noting.

Pressure. The initial pressure was usually elevated. There were five patients, however, in whom the initial pressure at the first lumbar puncture was essentially normal. In these five cases the leukocyte count in the fluid was elevated, even as high as 10,000 per cubic millimeter in one instance.

Table III

Findings in Initial Cerebrospinal Fluids Which Showed Essentially Normal Values for Sugar or Total Protein or Both

Case No.	Initial Cerebrospinal Fluid						
	Initial Pressure	Leukocyte Count	Smear	Culture	Sugar	Total Protein	Chloride
1	400	13,000	+	+	45	258	697
23	250	2,300	0	0*	44	23	729
24	600	7,400	+	+	43	252	702
26	—	1,900	—	+	82	13	725
31	400	1,062	+	+	20	42	693
41	100	927	+	+	51	22	716
43	—	14,000	+	—	125	222	681

Case numbers correspond to those in table 1 which contains additional data. Initial pressure is given in mm. of water. The values for sugar, protein and chloride are given in mg. per 100 ml. No sulfonamide therapy was used prior to lumbar puncture in any of these cases and only one of them had received parenteral fluids. (Case 43 was given 5 per cent glucose in physiological sodium chloride 3 hours before the spinal fluid was obtained.)

* MI obtained from nasopharyngeal culture.

Sugar and Protein. Although most of the cases showed the customary decrease in the sugar and elevation in the protein content of the cerebrospinal fluid in the first lumbar puncture, there were seven in which one or both of these values were essentially normal. The data in these cases are shown in table 3. Simultaneous blood sugar determinations were not done in these cases, but the urine in each instance gave a negative reaction for sugar with Benedict's solution. There seemed to be no correlation between the severity or duration of the illness and the normal sugar or protein values. As far as could be determined, none of these patients had received sulfonamide drugs or intravenous glucose prior to the initial lumbar puncture ex-

cept case 43. Such normal values have occasionally been observed in cases of meningococcic meningitis even prior to the introduction of sulfonamide therapy.[8]

Leukocytes. The leukocyte count in the initial cerebrospinal fluid varied from 72 to 48,000 per cubic millimeter and from 95 to 100 per cent of the cells were polymorphonuclears. The lowest count was obtained in a patient with the Waterhouse-Friderichsen syndrome (case 9) who proved to have only a slight meningeal reaction at autopsy. In one-third of the cases there were more than 10,000 polymorphonuclear leukocytes per cubic millimeter.

Bacteriology

Methods. Cultures of the cerebrospinal fluid were made on the surface of 10 per cent horse blood agar plates and also in beef infusion broth containing 1 per cent horse or rabbit blood. Occasionally some of the spinal fluid was incubated directly. Blood cultures were made by inoculating 10 c.c. of blood into 100 c.c. of beef infusion broth (pH 7.8). Incubation was carried out at 37.5° C. in a candle jar. Whenever feasible the materials were inoculated into warm media and incubated with a minimum of delay. Para-aminobenzoic acid was added to the media when cultures were made after the institution of chemotherapy.[9]

Failure to grow meningococci from the spinal fluid was most often the result of improper cultural technic rather than inadequacy of the media used or because of the mildness of the infection. One or more of the following conditions could have accounted for the absence of growth in some of the present cases: an inadequate amount of fluid (less than 1 c.c.); fluid left at room temperature or in a refrigerator for long periods before incubation; materials obtained after the institution of sulfonamide therapy and, in one case, thymol added to the fluid by error.

The method that proved most satisfactory for isolating meningococci from cerebrospinal fluid consisted of centrifuging 5 c.c. or more of the fluid at high speed, removing the supernatant fluid, adding 5 c.c. of blood broth to the sediment and incubating as already noted. On several occasions good results were obtained by incubating 2 to 5 c.c. of the spinal fluid directly. Each of these two methods gave positive results in a few instances in which blood agar plates showed no growth. Herrick[10] demonstrated viable meningococci in the ventricles with negative cultures from lumbar fluid. He also obtained positive cultures after repeated taps when an initial spinal fluid culture was negative. One might postulate from these observations that the best method of insuring a positive bacteriological diagnosis would be to draw off 15 to 20 c.c. of spinal fluid and use the last 5 c.c. for the gram stain and culture.

The identification of meningococci was carried out as follows: A gram-stained smear was made of the cerebrospinal fluid or of its sediment. If a moderate number of gram-negative diplococci were seen, direct typing was

attempted by the capsular swelling method with antimeningococcus typing serums.[11] If only rare organisms were seen, direct typing was again attempted with the organisms obtained from the cultures. It was not considered necessary to carry out any agglutination or fermentation reactions with strains showing specific capsular swelling with Group I * antimeningococcus serum.[12] The Group IIα strains,[13] which also gave positive quellung reactions with homologous antiserum, were further identified by sugar fermentations and by agglutination and then confirmed by Dr. Sara E. Branham of the National Institute of Health. The Group II strains were identified in the same manner as the IIα strains except that they did not give capsular swelling. The agglutination and fermentation reactions are considered essential for the identification of all meningococcus strains which fail to give type-specific capsular swelling because the gonococcus also may cause meningitis,[14] and the two organisms give cross-reactions in agglutination and complement fixation tests.[15] In many cases of the present series, the meningococci were identified directly from the spinal fluid by the quellung reaction, a procedure which is obviously of great advantage if treatment with antiserum is contemplated.

Results. The bacteriologic findings on admission are shown in table 1. The diagnosis was made by culture or smear of the spinal fluid in most of the cases. In one case (no. 8) presenting a classical picture of the Waterhouse-Friderichsen syndrome, lumbar puncture was not done but Group I meningococci were obtained from the blood culture. Two other cases having a characteristic clinical course of meningococcic meningitis are included although smears and cultures of their cerebrospinal fluid were negative for meningococci. In both of these cases there was a polynuclear pleocytosis in the fluid before and for three days after the institution of chemotherapy and the cultures of the original spinal fluids were probably faulty. In one of these cases (no. 23) type I meningococci were identified from a nasopharyngeal culture and the other (case 40) had a typical rash.

The gram-stained smear of the initial spinal fluid was positive for gram-negative diplococci in all except three cases in which this was done. In many instances this involved a careful and prolonged search of the sediment of a centrifuged specimen.

Blood cultures were made in 18 of the cases with the severest illness and in 15 of those with less severe grades of illness. These cultures were positive in 12 of the former and in five of the latter. The type of the organisms obtained from the blood and from the spinal fluid was the same in every case.

Types. The distribution of meningococcus types for each of the two years is shown in table 4. The strains from the cases of meningococcemia are also included. It is seen that six of the seven Group II strains were isolated in the first year and 24 of the 26 Group I strains were isolated dur-

* The designation "Group" instead of "Type" seems to be warranted at the present time according to a recent personal communication from Dr. Sara E. Branham of the National Institute of Health.

ing the second year. These findings are consistent with the observation, based on larger surveys,[16] that Group II strains are more prevalent in endemic cases and Group I predominates during epidemics. Even these small numbers suggest that either an epidemic was prevalent during 1941–1942 or that such an epidemic was due to occur shortly thereafter. Indeed, the incidence of meningococcic infections continued to increase in the months following the end of this study and the Group I strains continued to predominate.

TABLE IV

Meningococcus Types

Group	Sept. 1940 through Aug. 1941		Sept. 1941 through Aug. 1942		Total
	Cases of Meningitis	Cases of Meningococcemia	Cases of Meningitis	Cases of Meningococcemia	
I	2	0	18	6	26
II	5	1	1	0	7
IIα	0	0	3	0	3
Not typed	7	1	6*	0	14
Total	14	2	28	6	50

* One of the strains had morphological and cultural characteristics of meningococcus, but it did not agglutinate with any of the typing serums available to us.

Relation of Type to Severity. It has sometimes been stated that Group II meningococci are less virulent than Group I strains,[4, 17] and from this it is assumed that the clinical infection is less severe. There is no conclusive evidence, however, that the virulence of meningococci for mice, even of Group I strains,[12] is any index of their pathogenicity for man. In this small group of cases the Group II strains seemed to produce clinical infections which were equal in severity to those associated with Group I strains. Thus, four of the Group II cases were classified as severe and one of them died. Nor was the severity of the Group II cases due to unusual host factors; in only one of them was there any history of alcoholism and there were no complicating conditions in any of the others. It is of interest that Group IIα strains were obtained from a fatal case of Waterhouse-Friderichsen's syndrome and from a two months old baby who recovered.

TREATMENT

Most of the detailed procedures previously outlined for the treatment of meningitis [6] were followed whenever feasible. Sulfonamide therapy was started promptly, usually after the diagnostic lumbar puncture. Sulfadiazine was used in 35 of the cases; other sulfonamides were used in the remaining cases and for part of the time in four of the patients who received sulfadiazine. In two-thirds of the adult patients and in two infants the initial dose, and in some instances additional doses during the first day or two, were

given as the soluble sodium salt parenterally in 0.3 to 0.5 per cent solution in physiological saline, with or without 5 per cent glucose. The total dose and the duration of treatment in each case are shown in table 1. Fluids were given liberally so as to insure an adequate urinary output, and parenteral injections of glucose solution and saline were given if necessary. Antimeningococcus rabbit serum was given intravenously to three patients.

Drug levels obtained in different patients varied considerably. In those who recovered the average level of free drug in the blood was about 11 mg. per 100 c.c. after 24 hours of treatment, and this level was generally maintained during the first week. Cerebrospinal fluid levels averaged from 50 to 80 per cent of the blood levels.

Course after Treatment

The duration of fever and symptoms and the results of cultures taken after chemotherapy was started are shown in table 1. Clinical improvement was judged by the diminution of fever, changes in the mental state and in the general evidences of active infection. Such improvement was noted within 24 hours of the initial dose of sulfonamide in all but two of the patients who recovered. One of these two patients (case 11) had sustained a cerebral laceration as evidenced by the numerous red blood cells in the spinal fluid and a history of having fallen down stairs in his delirium prior to admission. His blood sulfadiazine level was only 1.4 mg. per 100 c.c. after 24 hours. An additional dose of 2.5 grams of sodium sulfadiazine was given intravenously during the second day and clinical improvement was evident on the next day when his blood level was still only 5.5 mg. per 100 c.c. The second patient (case 19) had an adequate blood level and was also given 60 c.c. of antimeningococcus rabbit serum intravenously.

Bacteriology. Cultures of spinal fluid obtained within the first 12 hours after drug therapy in three cases were all positive. A second spinal fluid 12 hours later was sterile in each of these patients and they all recovered. In five other cases, positive cultures were obtained from spinal fluid after 17 to 24 hours of chemotherapy. Two of these patients died about 24 hours later, although the fluid obtained shortly before death was sterile. In both cases the blood sulfadiazine levels were 17 mg. per 100 c.c. or higher, and antimeningococcus serum was used in one of them. In every case, once the cerebrospinal fluid became sterile, none of the subsequent cultures showed meningococci. Also, whenever the gram-stain of the fluid obtained after chemotherapy was started failed to show organisms, meningococci could not be isolated from such fluid. On the other hand, a number of fluids obtained after the treatment were positive in the gram-stain preparations but yielded no growth on culture. All blood cultures taken after sulfonamide therapy was started were negative.

Cerebrospinal Fluid Sugar and Protein (figure 1). The *sugar* content of the spinal fluid returned rapidly to normal after chemotherapy in most

instances, even with initial values as low as 8 mg. per 100 c.c. In only three cases were low values obtained after the first day of treatment. In two of these cases the blood sulfonamide levels were below 3 mg. per 100 c.c. during the first three days; the third patient (case 4) had a high blood level 12 hours after the initial dose but died after two days. In case 5, however, death occurred after two days of treatment and after the spinal fluid sugar had become normal. There were a few cases in which low sugar values were recorded several days after specimens with normal values had been obtained.

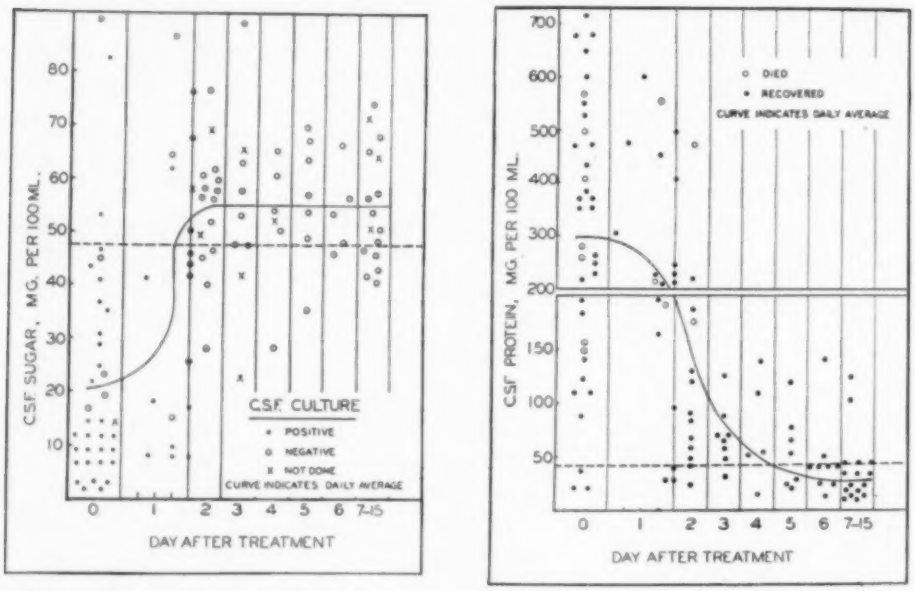

FIG. 1. Values of cerebrospinal fluid sugar and protein in relation to sulfonamide therapy.

In each instance, the fluid had been allowed to stand for more than a day before the determination was done.

It has already been noted (see table 3) that meningococci were occasionally isolated before treatment from spinal fluids having a normal sugar content, but this occurred in only one fluid obtained after the institution of chemotherapy. In cases of pneumococcic meningitis, numerous organisms have frequently been found in fluids with normal sugar and high drug levels.[18] Some of the fluids with low sugar values in this series yielded positive cultures, whereas others gave no growth.

The *protein* content of the cerebrospinal fluid decreased more gradually (see figure 1) and usually reached normal by the sixth day of treatment. In only one case did this value drop to normal after 24 hours of chemotherapy. In several individuals the protein values were still high after the sixth day of treatment, but this could be attributed in each instance to a traumatic puncture as evidenced by the large number of red blood cells in the

fluid. In no case was a normal protein value obtained while the patient was still delirious or comatose.

Thus, the sugar content of the cerebrospinal fluid gave no indication of the sterility of the specimen. A normal sugar value could not be relied on for prognosis and was not of any help in following the course of the disease or as an indication for cessation of therapy. The protein determinations, on the other hand appeared to be of some help in following the progress of the disease.

Complications

Post-infectious complications of a serious or permanent character were relatively infrequent. They were encountered in seven cases and included one case each of paresis or paralysis of the lateral rectus muscle, bilateral deafness, ataxia, cerebral thrombosis with transient hemiparesis, peripheral thrombophlebitis and pneumonitis with interlobar fluid. There was no instance of hydrocephalus. The patient with bilateral deafness failed to improve and there was some residual of the lateral rectus paralysis and of the ataxia. All the other complications were completely relieved before the patient left the hospital. One patient, 57 years old, who had a transient diplopia when he first regained consciousness was discharged well but returned 10 days later following a transient loss of consciousness. He then had a reactive depression from which he recovered in a few days. The pregnancy of two patients was unaffected by the disease or its treatment. Both of these patients subsequently gave birth to normal babies at term. The only significant toxic effect of the chemotherapy was drug fever. This occurred in three of the patients who were treated with sulfadiazine and in four who received other sulfonamides. This complication by itself was not considered to be an indication for discontinuing chemotherapy. One patient had a second attack of meningitis six months after apparently complete recovery. Group II meningococci were identified in the first attack but typing was not attempted in the second.

Mortality

There were nine deaths among the 43 cases of meningitis. Three of the fatal cases were 2½, 5 and 15 years old, respectively, and the other six were 35 or older. There were no deaths among the seven patients who were two years of age or younger, and these included three infants under one year.

None of the patients who died had symptoms for more than two days before entry and all lived only two days or less after treatment was begun. Sulfadiazine was used in eight of these cases and the ninth received sulfathiazole and sulfapyridine. Four of the patients died six hours or less after the first dose, and two others lived less than 14 hours after sulfonamide therapy was begun. Only two of the fatal cases had received the drug intravenously; they had adequate drug levels after 12 hours and died two days

later. One of these patients received 60 c.c. of antimeningococcus rabbit serum in addition. Both had sterile spinal fluid cultures before death. In two other patients the drug level was only 0.5 and in a third it was 3.8 mg. per 100 c.c. of blood 12 hours after the first dose.

Death in each case was associated with one or more of the following: extensive meningitis, encephalitis,[19, 20] increased intracranial pressure, bilateral adrenal hemorrhages, pneumonia or congestive cardiac failure. There was one case with the Waterhouse-Friderichsen syndrome proved at autopsy; another had extensive ecchymoses over the body and evidence of shock, but in this case no autopsy was done.

Three of the fatal cases were considered to be only moderately ill on admission and received their initial dose of drug orally. At varying intervals thereafter they suddenly became worse and died six, 12, and 26 hours after the first dose. There were no adrenal hemorrhages in these cases. One of these patients (case 3) had a temperature of 101.6° F. and pulse rate of 80 on admission and the latter rose to 90 after the initial lumbar puncture. Five hours later he rapidly developed signs of increased intracranial pressure, the pulse rate dropped to 50, and he died before a second lumbar puncture could be done. Postmortem examination revealed a not very extensive meningitis but a well-developed cerebellar pressure cone and marked cerebral edema.

Since patients may appear to be only moderately ill when first seen and yet die within a few hours, and since absorption of sulfonamides from the gastrointestinal tract may be quite variable,[21] it seems best to begin chemotherapy by the intravenous route in all patients with meningitis regardless of the clinical appearance of the patient.

Meningococcemia

The first authentic case of meningococcus septicemia was described by Gwyn in 1898 [22] in a patient with meningitis and arthritis. Shortly thereafter Salomon, in 1902,[23] reported a case of a patient who was admitted to the hospital four days after the onset of the disease. The meningococcus was recovered from the blood one week later, but it was not until two months thereafter that she developed meningitis, also proved bacteriologically, from which she recovered. This was the first recorded case of prolonged meningococcemia without meningitis. Until 20 years ago the diagnosis of chronic meningococcemia without meningitis was a rarity. In 1924 Dock [30] analyzed the features of 68 cases and in 1937 Carbonell and Campbell [17] analyzed 33 cases collected from the literature. There have been many reports elucidating particular features of meningococcemia such as endocarditis,[24, 25, 26] the skin lesions,[27, 28, 29] the quartan or tertian type of fever,[30, 31, 32, 33] or the occurrence of meningitis following prolonged meningococcemia.[34, 35] However, it was Elser in 1909 [36] and Herrick in 1919 [34] who stressed the extrameningeal features of meningococcic infections. Few of these authors

reported more than four or five cases which had come under their own observations over varying periods up to 10 years.*

Clinical Features of Eight Cases

It is noteworthy that in this small series there were eight cases of meningococcemia without meningitis. The ages ranged from two to 45 years. Lumbar puncture was done in only two of these cases; the other six had clinical features typical of meningococcemia and no definite signs indicative of meningeal irritation. One patient (C. W.) did have slight stiffness of the neck on anterior flexion on one day. Lumbar puncture was not done at that time but he became afebrile on the next day even before chemotherapy was started. None of the seven other cases had a stiff neck, and neither Dock [30] nor Carbonell and Campbell [17] mentioned this sign as a feature of their cases. It is possible that this was a very mild case of meningitis from which the patient was making a spontaneous recovery at the time chemotherapy was begun.

The disease in the cases of meningococcemia was very mild as compared with the majority of cases with meningitis. Only one patient was considered acutely ill, and even she was well oriented at all times. The only possible predisposing factor again was chronic alcoholism which was a feature of one case. The duration of symptoms varied from 12 hours to three weeks before admission to the hospital. It is impossible to tell in retrospect which cases would have developed meningitis or which would have gone on to spontaneous recovery or to chronic meningococcemia. The four patients who were admitted from 12 hours to two days after the onset of symptoms may, of course, have been in the prodromal stage of meningitis. Patients entering so soon after the onset of symptoms are often encountered in army camps or institutions where close supervision of health is maintained. This was pointed out by Herrick.[34] Forty per cent of his series of 315 cases entered before meningitis developed, and under serum therapy 5 per cent of the patients never did develop meningitis. Individuals recovering from meningococcemia without meningitis after eight months illness without therapy are on record [37] and one of Heinle's cases [38] probably had recurrent attacks over a period of 14 years. It is difficult to make a sharp distinction between acute and chronic meningococcemia. This is particularly so in the present cases, since the longest duration of symptoms in any case was only three weeks. However, Dock [30] considered cases to be chronic if the symptoms had been present more than one week.

The incidence of relevant symptoms and physical findings encountered in this series are compared with those in Carbonell and Campbell's [17] collected cases in table 5. In five cases there was both a *rash* and *myalgia*. This combination was present in a sixth case seen recently but not included

* Two series recently reported from army camps included larger numbers of cases of meningococcemia without meningitis: 32 cases in one series [45] and 13 cases in the other.[46]

in this series. *Arthralgia* was present in six cases. In Carbonell and Campbell's collected series there was also a high incidence of arthralgia but fewer cases had myalgia. It should be emphasized that only one of the patients in the present series had a mild stiff neck, but there were only three who were less than 20 years old, the age group in which meningismus occurs most frequently.[8] In evaluating the stiff neck as an indication of meningeal irritation one should be careful not to confuse it with the generalized myalgia which

TABLE V

Signs and Symptoms in Cases of Meningococcemia

Sign or Symptom	Carbonell and Campbell's Series of 33 Cases [17]	Present Series of 8 Cases
Rash	30	7
Myalgia	12	5
Arthralgia	23	6
Stiff neck	not mentioned	1*
Vomiting	6	4
Sore throat	5	3
Headache	17	3
Palpable spleen	not mentioned	3§

* Slight, improved before treatment was begun.
§ One of these patients was a chronic alcoholic and had a palpable liver in addition.

might involve the neck muscles. Such a myalgia occurred in only one patient, and meningitis was excluded in this case by the negative lumbar puncture findings. None of these cases showed anemia or general cachexia.

A useful diagnostic aid was the periodic type of fever, if it was present. There was one case each of the quotidian, tertian, and quartan type of fever respectively (figure 2). None of the cases showed the double quotidian fever of gonococcemia. However, this type of fever in gonococcemia probably applies only to the cases which have endocarditis,[39] although two of Futcher's cases[40] of gonococcemia without endocarditis showed it for periods of 48 hours.

The isolation and identification of the organism in the cases of meningococcemia were done in the same fashion as in the cases of meningitis. It should be stressed again, however, that the measures for the identification of the organisms which do not give a quellung reaction must be carried out in detail in order to exclude gonococcemia.

It is frequently stated and seems to be the consensus in the literature [26, 32, 38, 41, 42] that the blood cultures in meningococcemia are not positive until after the third week of the disease, or later. In the present cases the first blood cultures were always positive regardless of the time interval after the initial symptoms. Only one case had two negative blood cultures after admission,* but the collection of these cultures may have been faulty. Five blood cultures were positive even when taken on days when the recorded temperatures were normal for the entire day. It is, nevertheless, best to obtain blood for culture at the peak of the fever.

* Another such case was observed after the present cases were collected.

Treatment and Course (*figure 2*)

Six patients received sulfadiazine and two received sulfathiazole. These drugs were given by mouth in the usual doses. All except one recovered promptly. The delay in the recovery of patient M. D., aged 45, may

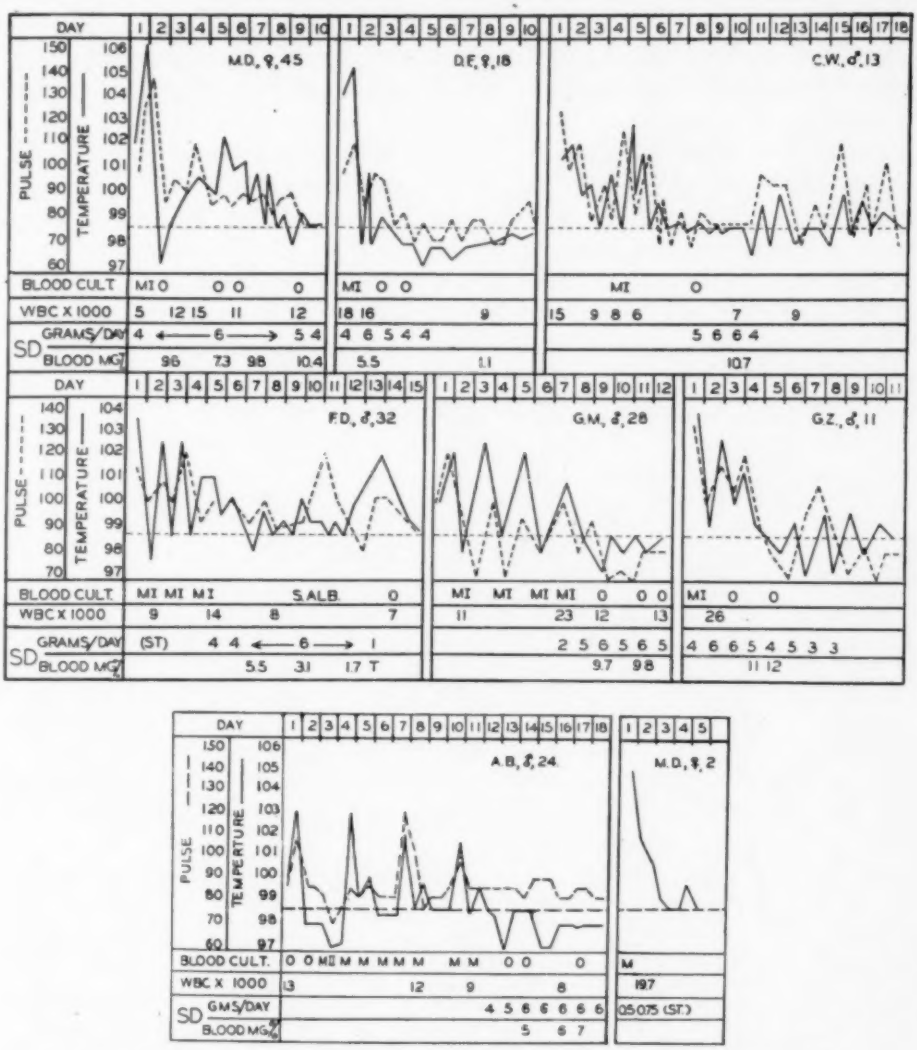

Fig. 2. Clinical charts of 8 cases of meningococcemia without meningitis. (For abbreviations see table 1.)

have been due to the severity of her infection, but it is more likely to have been due to the progressive dehydration secondary to inadequate fluid intake. Clinical improvement in this case occurred rapidly within 24 hours after the administration of parenteral fluids. The secondary rise in the fever of patient F. D. was a toxic reaction to sulfathiazole which subsided when the

drug was omitted. None of these patients had any clinical evidence of endocarditis. All recovered completely without any post-infectious complications, even the two year old patient M. D. who received only three doses of sulfathiazole. This patient was followed for a period of one and a half years after discharge and showed no evidence of further infection.

Differential diagnosis. The conditions with which this disease entity is most easily confused are gonococcemia with or without endocarditis, mild cases of meningococcal meningitis, or meningococcal endocarditis. It should no longer be confused with malaria, typhoid, typhus or rheumatic fever if careful history, physical examination, and laboratory studies are carried out. McLean [29] was able to stain the gram-negative diplococci from the purpuric lesions in 15 of his 18 cases. This may be a simple and frequently unappreciated means of rapid diagnosis in occasional patients before the organism has been isolated by cultural methods. Such purpuric lesions varying from extensive extravasation of blood to pin point petechiae were seen in the present cases. The method was attempted in some of these cases but without success.*

Comment

The protean character of the manifestations of meningococcic infections is well recognized, but that some of the cardinal clinical and laboratory features may be lacking in a given case needs further emphasis. In this small series there were cases of meningococcal meningitis in which fever, rash, or even stiff neck were absent. The initial cerebrospinal fluid pressure, sugar, protein and chloride were normal in some cases. Meningococci were isolated in one case from a cerebrospinal fluid with as few as 72 leukocytes per cubic millimeter. These findings occurred in a very small number of cases, but they seem to be of sufficient frequency to be of significance in the differential diagnosis from other central nervous system infections. The diagnosis can be made conclusively only when meningococci are identified and this requires careful cultural technic.

No specific criteria were found which could serve as a definite aid in prognosis when the patient was first seen. One cannot draw definite conclusions from such a small series but it would seem that patients who have a relative bradycardia on admission warrant close observation for the progression of signs of increasing intracranial pressure until the disparity between temperature and pulse rate no longer persists. Bradycardia was present on admission in one patient who appeared only moderately ill at the time but died six hours later, probably of increased intracranial pressure. This feature is also stressed because there are some [43] who advocate that lumbar punctures should not be repeated after the initial diagnostic tap. Although repeated lumbar punctures are not necessary in the therapy of all

* Since this paper was submitted the method has been carried out successfully in a few cases here and others have reported more regular successes.[47]

cases, the procedure still seems to be definitely indicated in occasional patients for the relief of increased intracranial pressure.

The majority of the patients who died received chemotherapy for less than 14 hours. In this series there are insufficient data to draw any conclusions as to whether antimeningococcal serum should or should not be used in conjunction with a sulfonamide. Nor are there enough cases to warrant deductions concerning the relative efficacy of the different sulfonamide drugs. Sulfadiazine appears to be less toxic than the other drugs and at least equally effective.

There is one phase of meningococcal infection which was recognized during World War I but which has not been emphasized in recent reports and yet deserves comment. This is the pulmonary manifestation of meningococcal infections. It was noted that 16 patients with meningitis had râles in the lungs without evidence of myocardial disease, and that two additional patients had rusty sputum. Occasionally these patients were diagnosed as pneumonia with pneumococcal meningitis until the studies on the spinal fluid had been carried out. Roentgenograms of the chest were taken in seven patients and five of these were interpreted as showing either early lobar pneumonia, bronchopneumonia or interlobar fluid. The other two were considered normal. Holm [44] in 1919 reported the autopsy findings of post-influenzal meningococcus pneumonia. This author had 23 cases of pneumonia without meningitis from which meningococci were obtained from the lung at post mortem (in pure culture in seven cases, and in mixed culture in 16 cases). There were also 13 fatal cases of meningococcic meningitis. In the latter group there was definite evidence of pneumonia in 10 and cultures of the involved section of the lung revealed meningococci in six (in pure culture in four cases, and associated with influenza bacilli in two cases). Gram-stained smears of the sputa from the pneumonia patients without meningitis showed a great many intracellular gram-negative diplococci, and meningococci were isolated on culture. Herrick [10] stated that in several of his cases of meningitis the onset was with acute pneumonia. He also reported [34] a patient with pleuritic symptoms who developed an empyema from which the meningococcus was grown and mentioned another case of bronchopneumonia following measles, in which the meningococcus was cultured from material obtained by lung puncture. These cases give ample evidence that the meningococcus can produce pneumonia. The rôle played by influenzal infection cannot be correctly evaluated without further studies.

Summary and Conclusions

Certain pertinent features of 43 cases of meningococcic meningitis and of eight cases of meningococcemia occurring in a period of two years beginning September 1, 1940 at the Boston City Hospital have been presented. There were nine deaths among the former and none among the latter. Sixteen cases occurred in the first year and 35 in the second.

Any one or more of the characteristic findings of meningococcic meningitis may be absent in any given case.

A tentative diagnosis of meningococcic meningitis can be made in almost every instance by examination of a gram-stained smear of the cerebrospinal fluid or its sediment.

Group II meningococcus should be carefully distinguished from the gonococcus especially in cases in which the organism is recovered only from the blood. Group II infections predominated in the first year and Group I in the second.

All except two of the cases with meningitis who recovered showed objective signs of clinical improvement 24 hours or less after chemotherapy.

The initial dose of sulfonamide should be administered intravenously to cases of meningitis even if they appear only moderately ill when first seen.

Patients with a relative bradycardia even though they appear only moderately ill on admission should be observed closely for evidence of increased intracranial pressure. Lumbar puncture still has a place in the therapy of meningococcal meningitis for diagnosis and for the relief of symptoms of increased intracranial pressure.

Normal cerebrospinal fluid sugar values obtained after the use of sulfonamides or of parenteral glucose therapy are of no value by themselves in estimating the progress of the disease.

Pulmonary involvement is quite frequent in the course of meningococcic meningitis. It probably represents a local infection by the meningococcus, either alone or with other organisms. Pneumonia due to the meningococcus may occur in the absence of meningitis, but such cases were not recognized in the present series.

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SOME CLINICAL ASPECTS OF MENINGOCOCCIC INFECTION *

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The purpose of this paper is to call attention to some of the less known or frequently forgotten manifestations of meningococcic infection. Those of us who, as a rule, see only one or two cases of this disease a year, are accustomed to think of meningococcic infection in terms of the textbook picture of acute cerebrospinal meningitis, with fever, perhaps a chill at onset, severe headache, rigidity of the neck and positive Kernig's and Brudzinski's signs. We are aware that a rash may be observed in some instances. Such, indeed, was my own impression prior to joining the Army. Since then, as a result of experience gained by observing a considerable number of patients in the hospitals of two Service Commands, my conception of meningococcic infection has been appreciably altered.

To be sure, many patients present the usual picture of acute cerebrospinal meningitis. When the disease is well established, it causes no difficulty in diagnosis. But because of the desirability of early treatment, diagnosis must be made early and this is by no means always easy. Furthermore, and this fact is often forgotten, cases of frank cerebrospinal meningitis constitute only a portion of the cases of meningococcic infection which will be encountered in any epidemic, large or small. Some patients with meningococcic infection recognized and treated early apparently recover, thanks to the sulfonamides, before meningitis has time to develop; others die before the appearance of meningitis, and in still others the organism fails to localize in the meninges. Because of the frequency of the non-meningitic forms, the diagnostic term "acute cerebrospinal meningitis" should, in my opinion, be discarded. Meningitis should be regarded simply as one of the manifestations of generalized meningococcic infection. One should think in terms of meningococcic infection, with meningitis, with arthritis, with pericarditis, etc., just as one thinks and speaks of syphilis as a blood stream infection, with vascular, cerebrospinal, skin or joint localization. Occasionally there appears to be no localization.

The sporadic case of meningococcic infection without meningitis, which might crop up in the absence of an epidemic, is likely to be overlooked, and with justification. When the organism is prevalent, however, as it has been during the past two winters in both military and civilian communities, non-meningeal cases should be recognized, and such patients can be saved if the physician is constantly on the alert and does not forget that they occur.

* Read at the Regional Meeting of the American College of Physicians, Columbus, Ohio, May 14, 1943.

Before proceeding with a description of the more common clinical syndromes, it might be worth pointing out that we are still in the dark concerning the epidemiology. Case to case contacts can rarely be traced and in only a few instances has there been any concentration of cases in a small, closely knit group. In most of the camps, distribution has been spotty. We do know that if a high carrier rate is found in an organization, cases are likely to appear, yet the degree of intimacy of contact with a carrier or with an actual case does not seem to determine which man will next acquire the disease. Probably there are different degrees of virulence of the organism or different degrees of individual susceptibility, or both. It is likely that most persons are relatively immune and can harbor the organism without acquiring the disease. The organism perhaps passes through many hosts before it reaches one in which conditions are suitable for development of the disease. For the most part, meningococcic infection has tended to follow in the wake of an epidemic of upper respiratory infection. It is more prevalent among newly inducted troops than among seasoned soldiers. Upper respiratory infection, crowding, fatigue, and exposure to the elements are contributing factors; they render the individual susceptible when otherwise he might, for a time, harbor the organism without getting sick. This is so striking that one could almost postulate that the meningococcus is ordinarily non-pathogenic and becomes pathogenic only when circumstances have fertilized the ground. The prophylactic use of sulfadiazine in large bodies of troops has been tried in certain camps. Whether it has been effective in reducing the carrier or disease rate will doubtless be reported at a later date.

What forms can meningococcic infection take? Time does not permit detailed discussion of the various clinical pictures and all one can do is outline very briefly what should be looked for.

First, a large proportion of patients, irrespective of the form which meningococcic disease will take, complain initially of cold in the head, sore throat, cough, or other respiratory symptoms of a few days' duration. In fact, it is common for them, on admission to the hospital, to be sent to wards allocated for acute nasopharyngitis. Such a patient may remain there for a few hours, or perhaps a day or more, before the development of some new symptom or sign provides the clue to proper diagnosis.

Meningococcemia with Acute Meningitis

This term refers to the ordinary case of acute cerebrospinal meningitis. The early and important indications are: headache more severe than usually experienced in upper respiratory disease alone; an apathetic state, with a desire not to be disturbed, or its opposite, striking restlessness; and slight stiffness of the neck, subjective or objective. Deep muscle aches, especially in the extremities, are important. The temperature may be elevated, but is not necessarily in the higher range. An eruption may or may not be present or develop subsequently. Evidence of arthritis may or may not occur; joint

manifestations may appear before those of meningitis. In an occasional case nausea, vomiting, and profuse diarrhea will be the outstanding initial symptoms; they may quite overshadow the more typical manifestations. The leukocyte count is usually high; in the early stages it may be normal. The polymorphonuclear leukocytes will be increased. It cannot be too strongly emphasized that one must not wait for the so-called typical signs, such as the Kernig's or Brudzinski's responses or opisthotonos. Meningitis must be suspected on the basis of these earlier manifestations when they are more striking than one would expect with an ordinary respiratory infection. A diagnostic lumbar puncture should then be performed. When a tap is done early, the spinal fluid may show a few cells, perhaps not over six or eight, but these are almost enough for diagnosis. A second tap a few hours later will show a decided increase in cell count. Organisms may or may not be found; sometimes they will be seen before the appearance of leukocytes. Blood culture may or may not be positive, but because of the importance of early treatment, one cannot afford the time required for the organism to grow before establishing diagnosis.

Not infrequently the onset will be much more sudden, with unconsciousness developing within a few hours after the onset of mild headache and fever. For example, a young officer seen in one of the camps complained at bedtime of having a slight headache and feeling "grippy". On the following morning he was found unconscious under the bed. Prompt recognition of the disease clinically, and substantiation by immediate lumbar puncture, resulted in prompt and life-saving treatment.

Occasionally an acute psychosis, most likely of the maniacal type, will be the first and only symptom. I have seen two such cases admitted to psychiatric wards and kept there for a day or so before the true nature of the trouble was discovered. Lumbar puncture to exclude meningitis is indicated in any case of psychosis developing suddenly and without obvious cause, even in the absence of temperature elevation.

Acute Fulminating Meningococcic Septicemia

Cases of this form of the disease are almost certain to appear in any epidemic. What happens to the patient seems unbelievable until one has personally observed such a case. Characteristically, the onset is similar to that of acute respiratory infection. Suddenly, however, the picture completely changes. The temperature, previously 99 to 101° F., will rise to between 104 and 107° F. The patient becomes obviously much sicker with astounding suddenness. A generalized eruption will appear. Many medical officers have told me they could actually see the eruption developing, actually see the spots appear. In short order, perhaps one or two hours, sometimes longer, the signs of peripheral circulatory failure develop; the patient becomes cold, clammy, pulseless, shows rapid fall of blood pressure, and dies within several hours. Until near the end he is conscious and rational;

perhaps, but not necessarily, restless and apprehensive. Loss of consciousness supervenes a short time before death. The picture is similar to that of severe surgical or traumatic shock. Occasionally these patients, with no history of feeling ill beforehand, will collapse at work or in their bunks and be dead within a few hours. The eruption is characteristically petechial, but contrary to the usual teaching it is not necessarily so. Very often the lesions resemble the rose spots seen in typhoid fever, but are more numerous. The petechial spots may merge and form areas of ecchymosis.. A rapidly rising leukocyte count is the rule.

In this type of case meningeal symptoms are not common, nor are there any signs of meningeal irritation. Lumbar puncture will reveal a normal fluid. These facts are extremely important; unless they are borne in mind, diagnosis will be missed. It will be missed because the physician thinks only in terms of meningitis. Blood cultures should be positive and usually are; but again one cannot wait for blood culture before instituting treatment. Sometimes meningococci can be demonstrated by staining with gram stain a film of the tissue juices obtained by scratching or gently squeezing a skin lesion. Occasionally they can be seen in the leukocytes of an ordinary blood film stained with gram stain. Diagnosis can sometimes be confirmed by one of these methods, when both blood and spinal fluid cultures are negative.

This is the picture of the Waterhouse-Friderichsen syndrome. As originally described, such cases at postmortem examination showed hemorrhage into both adrenal glands. In those which I have seen autopsied, some have shown adrenal hemorrhages, others have not; but the course of the disease in the two instances is the same.

A typical history of this form of the disease is as follows:

A soldier was admitted to the respiratory ward of a station hospital at 10 a.m. with a temperature of 101° F., and a history of nasopharyngeal symptoms for the previous day or so. Physical examination showed nothing of importance. At 4 p.m. his temperature was 105° F., and he seemed much sicker. An alert nurse discovered on his chest and abdomen an eruption which had not been there when he was examined by the ward officer in the morning. He was seen almost immediately by the medical officer and found to be in circulatory collapse, cold, clammy, with rapid, barely perceptible pulse and barely obtainable blood pressure readings. Sulfadiazine therapy was started immediately; it was closely followed by blood plasma and glucose-saline infusions. The patient was dead two hours later. Postmortem examination revealed extensive hemorrhages in both adrenal glands.

Meningococcemia with Arthritis

This form, although acute, lacks the overwhelming intoxication just described. As already pointed out, involvement of joints can and does occur in the meningitic case. In the non-meningitic case a history of prodromal respiratory symptoms is the rule, but the patient will also complain of joint

pains with or without swelling and redness. The larger joints, especially the knees, are most likely to be affected. Careful questioning will probably elicit a story of deep muscle aching in legs and arms. An eruption is almost invariably present. It is more often macular than petechial. It is scanty compared to that seen in the fulminating case; the spots must often be searched for. They show a tendency to be distributed over the hands, wrists, feet and ankles, or they may be confined to the palms or soles. Sometimes they appear only in the region overlying the pectoral muscles or the anterior chest and abdomen. These cases are readily and justifiably confused with acute rheumatic fever or other joint diseases. The important differential features are the eruption, scanty though it may be, a greater elevation of leukocyte count than usually occurs in acute rheumatic infection, and a history of muscle aches, especially in the arms and legs.

Lumbar puncture will reveal a normal fluid. Blood culture may or may not be positive. In the doubtful case the effect of a sulfonamide drug must be tried.

A soldier was put off a train for medical treatment at a camp in Alabama in the morning. He was a member of a convoy which had left a post in Missouri about 24 hours previously. He felt well at the time of departure and during the first day out. During the night he had become feverish, thirsty, and developed a headache. His knees began to ache. He spent most of the night working his way back and forth from his seat to the water cooler by using his hands for support on the arms of the seats. On arrival at the camp hospital he had a high fever, minimal signs of meningitis, a typical eruption, and acutely tender, swollen knees. He recovered following treatment with sulfadiazine. Another soldier was admitted to a hospital because of a "sprained ankle" and was under observation on an orthopedic ward for two days. There was no history of trauma, but he thought he might have hurt the ankle while standing guard two nights previously. He had had a "cold in the head" for a few days, and there was slight fever. The right ankle was painful, slightly swollen, red, and tender. Leukocyte count was elevated. A medical consultant discovered a few macules on both soles. The patient was treated with sulfadiazine and recovered in two days. Blood culture taken before starting treatment subsequently showed meningococci.

At another station hospital a twenty-year old soldier was admitted with a diagnosis of acute rheumatic fever. Three days prior to admission he had developed feverishness and aches and pains in his leg muscles. He had had a stuffy nose and sore throat for a week. On the day before admission his left ankle and both knees became acutely painful, swollen, and red. A generalized maculo-papular eruption was observed over the trunk and extremities. Temperature was 100° F. White count was 21,600. Three days after admission all joints were stiff and sore, and in spite of salicylate therapy, he was generally worse. At this time the diagnosis was changed to probable meningococcemia. Salicylates were stopped and sulfadiazine was started. After two days of treatment with this drug the soldier was entirely

well. Blood cultures were negative. In my opinion, irrespective of the negative blood culture, this is a typical case of meningococcemia.

Chronic Meningococcemia

This is a less malignant form of meningococcic infection. It is characterized by intermittent bouts of fever with the typical eruption and usually pain, swelling, and tenderness of one or more joints. If untreated, the patient may recover from the attack only to experience repeated similar episodes at intervals of weeks or months. The eruption in these cases is rarely intense and may well be overlooked, especially when it is limited to the distal parts of the extremities. Sometimes lesions resembling those of erythema nodosum appear on the extremities. A typical attack of acute cerebrospinal meningitis may set in during any of the febrile episodes, or the disease may continue as a chronic bacteremia for months.

Treatment

The response to sulfonamide drugs is little short of miraculous. A patient who seems to be *in extremis* often will recover completely within as short a time as 36 to 48 hours. Whereas in epidemics during the last war the mortality was as high as 50 to 75 per cent, it is now roughly between 7 and 10 per cent in various military and civilian hospitals. In some regions it has been as low as 2 per cent. As in any form of acute infection, the earlier treatment is started, the more favorable is the response. Complications are rare except in tardily treated cases.

No dogmatic rules may be laid down for administration and dosage. Sulfadiazine at present is regarded as the drug of choice, with sulfathiazole a close second. The first dose should be given intravenously. The patient's condition can change so rapidly that there is no justification, once the diagnosis has been made, for losing the time it takes for an oral dose to become absorbed. It is often wise to give at the start more than the standard 5 gram dose; 6, 7 or even 8 grams can be readily tolerated. For intravenous administration the drug should be dissolved in the prescribed amount of distilled water, not in a dextrose or saline infusion. If the patient is not unconscious or vomiting, subsequent doses may be given orally. The initial oral dose should be given immediately after the intravenous dose. If the patient is vomiting or unconscious the intravenous method should be continued, or the drug may be administered subcutaneously. One cannot be dogmatic about the optimum blood level. Recovery is not uncommon in patients whose blood levels have not exceeded 5 to 6 mg. per cent, yet one would prefer a level of at least 10 mg. per cent. In severely ill patients a level of 12 to 15 mg. per cent, or even higher, should be maintained if possible.

The importance of fluid intake must be stressed. Any patient receiving a sulfonamide should be given enough fluid to insure a 24-hour urinary output of at least 1500 c.c. The fever and sweating in these cases may make necessary an intake as high as 3500 to 4000 c.c., in order to keep output at this level. If this schedule is maintained, the possibility of renal complications due to the drug is reduced to the minimum, but with a low fluid intake renal shut down is a definite and dangerous possibility.

The sulfonamide drugs are, unhappily, not as effective in the cases of fulminating septicemia. These cases, and those of frank meningitis, which are recognized and treated late, account for most of the deaths. When the patient is overwhelmed from the start there appears to be hardly time for the drug to take effect before he is dead. In such cases anti-meningococcic antitoxin is being advised and tried as a supplementary measure in the hope that what we believe is an overwhelming toxin may be neutralized by antitoxin, and the patient thus kept alive long enough for the sulfonamide to get in its effect. I am not prepared to say whether antitoxin has been shown to be worthwhile, but for the time being expect to continue recommending it in the fulminating cases. Blood plasma and adrenal cortical extract are also worth trying in the fulminating case; they might help tide the patient over a period of circulatory collapse and provide time for the antitoxin and the sulfonamide to take effect. An initial dose of 10 mg. of adrenal cortical extract can be given intramuscularly with safety and can be followed by 5 mg. every three hours for as long as three days, but no longer.

Summary

1. Meningococcic disease should be regarded as a blood stream infection, of which cerebrospinal meningitis is but one of the manifestations. Cases without meningitis are common. Early diagnosis is imperative. When the disease exists in a community every case with upper respiratory symptoms should be regarded with suspicion and closely watched.

2. The usual forms in which meningococcic disease may appear are:

a. Meningococcemia with acute meningitis. Diagnosis can and should be made before the appearance of the textbook signs of meningitis. Especially in the presence of upper respiratory symptoms, severe headache, apathy, restlessness or delirium, muscle aches, slight stiffness of the neck, or an eruption which is not characteristic of the common exanthemata, is an indication for diagnostic lumbar puncture.

b. Acute fulminating septicemia with or without meningitis, manifested by sudden onset with marked prostration, rapidly developing profuse macular and petechial eruption, early and rapid circulatory collapse followed by death, often within a matter of hours.

c. A less severe form of bacteremia characterized by inflammation of one or more joints, a less intense eruption, often macular rather than petechial, and aching in the muscles of the extremities.

d. A chronic form of bacteremia, in which bouts of fever, accompanied by joint pains and mild eruption, occur at intervals of weeks or months with intervening periods of relative good health.

In any of these last three groups the clinical picture of meningitis may develop, but the diagnosis can and must be made in the absence of symptoms or signs of meningeal involvement.

3. Early treatment with a sulfonamide drug is almost certain to effect a cure except in cases of acute fulminating septicemia and in cases predominantly meningitis in which treatment is started late. The first dose should be given intravenously. The condition of the patient is the best guide to subsequent doses. Fluid intake must be high, in order to insure adequate urine output. Anti-meningococcic antitoxin should be tried in all severely ill patients. Adrenal cortical extract may have a place in the treatment of the circulatory collapse associated with the fulminating septicemia.

ANALYSIS OF AN EPIDEMIC OF DENGUE FEVER*

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The following paper attempts an analysis of 318 cases of dengue fever. The authors wish to emphasize that in this area there was no possible recourse to literature on this subject other than that contained in a few available standard textbooks. Approximately 1200 cases of dengue fever occurred in army personnel in and around a coastal town on an island in the South Pacific from March 1, 1943 to April 30, 1943. At the present time, May 10, 1943, there is evidence of a minimal degree of subsidence in this epidemic. The incidence in the total army command on this island can not be given at this time since this would disclose military information. Concurrently the number of cases among the civilian population of this coastal town, where dengue fever is endemic, paralleled the incidence among army personnel. This outbreak was preceded by epidemics of the same disease on other South Pacific Islands in the vicinity. Six hundred and twenty-two of the cases occurring on this island were hospitalized during the interval of time mentioned above. Three hundred and eighteen cases of this latter group fulfilled sufficient criteria to warrant careful analysis and statistical survey.

The following criteria were strictly observed in the consideration of the cases to be included in this survey. All cases were seen by an army physician not later than 24 hours after the onset of the illness. Thereafter the clinical course was followed carefully, and temperature and progress notations were made at frequent intervals. None of these cases had been exposed to malaria. All cases who had received any sulfonamides prior to onset, at onset or during the course of the illness were excluded.

Dengue fever is an acute infectious disease caused by a specific filterable virus and transmitted by the bite of a mosquito. It is manifested clinically by an incubation period of six to 10 days, a sudden onset with chilliness, generalized aching and pain, especially in the back and to a lesser degree in the extremities, severe frontal and postorbital headaches, weakness, insomnia and malaise. The rise in temperature is rapid and may be "saddleback" in type, characterized by a primary elevation for three to four days followed by a period of remission or intermission for 24 to 48 hours and finally a secondary elevation for two to three days. This febrile response is associated with a relative bradycardia. A rash may occur both in the primary and the secondary phase of the illness. This disease is associated with complete recovery, except for an occasional death in very elderly patients. However, the convalescence may be prolonged and accompanied by marked weakness, and physical and mental depression. There is a pronounced leukopenia, a

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relative lymphocytosis and a Schilling shift to the left. Numerous reports of different epidemics and careful analysis of any one epidemic attest to the marked variability of the clinical manifestations of this disease, especially insofar as the degree of illness, the temperature curve and the rash are concerned.

The name dengue fever or dandy fever is reported to be derived from the spanish term for a dandy, or "Denguero," one who walks with a dandified, mincing gait. The supposition is that the pain and aching in the back and extremities cause this abnormal type of gait. The terms breakbone fever and bouquet, the latter being descriptive of the rash, are also frequently used.

Dengue fever occurs predominantly in tropical and subtropical regions. It may occur in epidemic form in any area where there is a suitable numerical relationship between the number of proper mosquito vectors, the number of cases, and the number of nonimmune individuals. It frequently occurs in coastal towns probably because this type of locality is most heavily infested by the *Aëdes aegypti* mosquito which is the commonest vector. It is a very common disease in the South Pacific Islands, Australia, the Orient and the Caribbean Islands. In the United States it is frequently seen in the Atlantic and Gulf coastal plains. Epidemics have been reported as occurring in New York, Philadelphia, Charleston, South Carolina, Florida and Texas. Benjamin Rush was one of the first to describe this disease as occurring in epidemic form in Philadelphia, in 1780.

The etiological agent of this disease is believed to be a filterable virus which is present in the patient's blood for a period of 12 to 24 hours prior to the onset of clinical symptoms through the second or third day of illness. At some time during these three or four days the proper mosquito vector must bite the patient to obtain the virus and become infected. After the ingestion of virus-containing human blood by the mosquito, a period of eight to eleven days must elapse before it can transmit the disease to a nonimmune individual. The mosquito remains infective from the ninth, tenth or eleventh day to the end of its natural life span and is apparently unaffected by harboring the virus. As is the case in all mosquito borne infections, it is the female mosquito alone which bites in an effort to get blood supposedly necessary to complete the process of ovulation. The male mosquito has only rudimentary biting organs which cannot penetrate the skin, thus relegating him to feed on the nectar of plants and other vegetable matter.

The *Aëdes aegypti* (*Stegomyia fasciata*) and *Aëdes albopictus* (*Stegomyia scutellaris*) are the most frequent transmitting agents of the virus of dengue fever. *Culex fatigans* (*Culex quinquefasciatus*) and *Aëdes taeniorhyncus* have been mentioned as possible vectors. Three common types of mosquito found on this island are the *Aëdes aegypti, Aëdes taeniorhyncus* and *Culex fatigans.* It is felt that the principal vector agent in this epidemic is the *Aëdes aegypti* mosquito which is an urban coastal dweller, a daylight biter and frequents the habitations of man. Many of this species of mosquito

were caught in the homes of this coastal town during the epidemic and were found breeding in tin cans, water barrels and other artificial containers which had been discarded and were partially filled with rain water. The occurrence of this epidemic during March and April is significant because it coincides with the period of greatest mosquito prevalence in this area, which exists during and for a few months after the more rainy season in February, March, April and May. At the onset of this epidemic some observers felt that the very prevalent *Aëdes taeniorhyncus* was the principal vector, but final opinion incriminated the equally prevalent *Aëdes aegypti*. The *Aëdes taeniorhyncus* is primarily a rural, salt marsh breeder and has an unusually long range of flight. All the cases in this epidemic had apparently contracted the disease while living in or visiting the city. In no case was anyone infected who lived even three miles outside of the city limits and had not visited the city. In addition, only a few recent reports incriminate the *Aëdes taeniorhyncus* and all authorities are in agreement as to the potentiality of the *Aëdes aegypti* as the most efficient vector.

Susceptibility to this disease is apparently universal. Various observers of previous epidemics differ as to the relative period of immunity which is conferred by an attack of dengue fever. The current opinion on this point ranges from five to 10 months. After several attacks a more lasting immunity is believed to exist. One case was observed early in the epidemic who had an attack characterized by a saddle-back fever, rash and the usual convalescence. Approximately two months after the first attack this individual became ill with fever and a rash a second time. During the interim he had been visiting in the same town, which is the seat of this epidemic and had been exposed again to the mosquito vector.

Little is known as to the characteristic pathologic lesions in this disease and since this epidemic has been attended by no mortality, investigation of this feature was not possible. Again we must emphasize the lack of available literature at the present time to study the previous reports of this disease.

At the present time the diagnosis of dengue fever depends primarily on an evaluation of clinical findings and blood examination. A high index of suspicion is necessary to make the diagnosis early in an epidemic and especially in those epidemics characterized by many atypical findings. On a neighboring island, where malaria is quite predominant, a sudden increase was noted in the number of febrile cases and although in the majority of instances the blood smears were consistently negative for plasmodia, they were given antimalarial drugs and classified as cases of malaria. Two or three weeks later the characteristic features of dengue fever had occurred with sufficient frequency to cause a change in diagnosis in practically all of these cases.

The common diseases to consider in differential diagnosis are influenza, measles, scarlet fever, malaria, meningitis, typhoid fever, salmonella infections and yellow fever. Influenza is almost invariably associated with a

definite respiratory involvement, marked cyanosis, and is not characterized by a rash. Measles is characterized by an early severe coryza and a definite rash appearing initially on the face. The mild pharyngitis which was observed in occasional cases in this epidemic was not a confusing factor. Scarlet fever is characterized by leukocytosis, tachycardia and the constant presence of pharyngitis. The periodic chills of malaria and the presence of the malaria parasite in the blood film serve to distinguish the two diseases. The severe frontal headache and, in a few instances, a slight cervical rigidity in our series of cases suggested the diagnosis of meningitis. However, in the latter disease the constant and definite cervical rigidity, tachycardia and leukocytosis serve as differentiating points. The relative bradycardia and rash of typhoid fever may be confusing. However, the prolonged febrile course, the palpable spleen, positive Widal agglutination test, blood, stool and urine cultures aid in a differential diagnosis. Many authorities stress the similarity of dengue fever and yellow fever. The heavy, persistent albuminuria and jaundice of yellow fever are listed as differentiating factors. There are other less common virus diseases which are reported to be difficult to differentiate from dengue fever. Among these are pappataci fever (phlebotomus fever) and Rift Valley fever. The authors of this report have had no experience with these diseases and, therefore, shall not attempt to point out the possible differential characteristics.

Prevention of the spread of this disease rests almost entirely upon isolation and screening of any cases, especially during the first five days of illness, and mosquito vector eradication and control.

Since no specific therapy is known, symptomatic care is indicated. Alcohol or cold water sponges are helpful during the febrile episodes. Codeine, aspirin and phenacetin may be used to relieve the headache and generalized pains, and in a few instances the administration of hypodermic injections of morphine is indicated. Mild sedation is of value for the insomnia which may occur.

This epidemic of dengue was characterized by a relatively mild clinical course and only a small percentage of cases manifested a marked degree of toxemia. However, the frontal headache, backache, eyeache, febrile reaction and prolonged convalescence caused much discomfort and temporary incapacitation.

All cases upon analysis were found to be living in this coastal city or the vicinity. Those cases who became ill in the outlying areas had visited there in the fortnight previous to onset of illness. Since no cases were encountered who had not given a history of having been in this city, the incubation period was thereby definitely determinable in six cases since they had visited there only once previous to onset of clinical symptoms. The range was from six to 10 days, averaging seven and one-half days.

These cases were characterized by a sudden onset in 298 instances or 93.7 per cent. This, however, was not constant since 20 cases or 6.3 per cent were singularly vague as to the approximate time of onset. The usual

initial complaints were a sudden onset of feverishness, chilly sensations and excessive perspiration. Repeated episodes of chilliness were complained of during the first 24 to 48 hours by 101 cases or 31.8 per cent but no definite shaking chills were experienced. The rise in temperature was early and rapid but rarely exceeded 104° F. This was followed in the next few hours by severe supraorbital or frontal headache, eye pain, backache and generalized muscular aching. Early in the course of the illness the flushed facies and reddened eyes were very striking, and 83 cases or 26 per cent showed this change. This cutaneous flush sometimes extended down over the neck and chest and was out of proportion to the degree of elevation of temperature. The flushing of the face and congestion of the ocular conjunctiva gradually subsided but the cutaneous flush over the chest frequently was converted into the first real manifestation of a rash. One hundred and eighteen cases or 37 per cent developed a definite rash irrespective of the type of temperature curve. This rash was extremely variable in its time and site of appearance but, for the most part, was characterized by a blotchy, confluent, wide spread, macular erythema which covered the chest, often extending to the abdomen and shoulders. Except for the initial evanescent facial flush, an actual rash never involved the face and only very rarely involved the base of the neck. Many examiners described this rash, which covered the chest, as morbilliform or measles-like. This rash seemed to fade slightly during the remission, only to be accentuated at the time of the secondary elevation of temperature and to spread to or be accompanied by a rash on the extensor surface of the hands, wrists, forearms, feet, legs and ankles. Frequently, this rash, which usually occurred in the second half of the illness, began distally and spread proximally along the extremities. It was difficult to determine the relationship of the secondary rise in temperature to the extension or exacerbation of the rash. Many observers have said that the secondary rise of temperature drops suddenly upon the reappearance of this rash. However, in this series of cases there were instances in which the secondary rise in temperature preceded, coincided with or followed the rash. This secondary rash was macular, maculopapular or scarlatiniform and sometimes covered the trunk and extremities. Punctate petechial hemorrhages occasionally occurred in the center of these areas. This secondary rash may or may not be followed by a fine desquamation. This was seen in relatively few cases. Palpation of the chest and extremities elicited a definite hyperesthesia, and itching of the skin was an occasional complaint.

The temperature curve was of the classical saddle-back variety in 210 cases or 66 per cent. The initial rise was rapid and lasted for three to four days, rarely exceeded 104° F., and was followed by a definite remission or frequently an intermission of 24 to 48 hours. This was followed by a secondary elevation in temperature for about 36 to 72 hours, which rarely rose above 103° F. In most cases the terminal drop of temperature was rapid and was associated with much sweating. Many of the cases with a saddle-back type of temperature curve displayed a higher elevation on the

first rise than on the second rise. However, there were a few cases showing an increased elevation of two degrees in the secondary febrile episode as compared with the primary episode. Ninety-four cases or 29.5 per cent exhibited a single rise in temperature which lasted five to six days with slight diurnal variations. An interesting phenomenon was observed in 89 of the 318 cases in that they exhibited a reversed diurnal variation of fever with a higher temperature from 8 a.m. to 2 p.m. than from 2 p.m. to 10 p.m. Those cases showing a saddle-back type of temperature ran a febrile course of six to eight days. Those cases with a single rise of temperature lasted about five to six days. There were 10 cases which we considered afebrile. These were carefully watched from the onset of illness and were characterized in two instances by rash and in all cases by generalized aching pain, retrobulbar pain, leukopenia and a Schilling shift to the left. They were not as toxic as the febrile cases.

The frontal or supraorbital headache was the most common complaint and was frequently associated with backache, generalized aching and eyeache. Deep eye pain or retrobulbar pain accentuated on movement of the eye was experienced by 80 patients. Few complained of actual joint or bone pain, but two complained bitterly of severe aching around the knees. The pain may best be described as a severe continuous aching and seems to exist in the deep muscle structures and at the tendinous insertions of the muscles. No cases of actual arthritic pain or ache were seen, and mild active and passive movement of joints was not associated with any marked increase in pain. Paravertebral aching was common and was most severe in the upper dorsal and lumbar regions. Only three cases complained of no aches or pains but revealed sufficient stigmata of the illness, such as febrile reaction, leukopenia, malaise and rash, to warrant inclusion. The cases of saddleback temperature enjoyed a partial respite from pains and aches during the remission stage and were more comfortable during this time, only to be smitten again with pain coincident with the onset of the secondary rise in temperature. The secondary phase of aching was not so severe as that accompanying the initial rise in temperature. Superficial palpation elicited hyperesthesia in 20 cases or 6.3 per cent. Deep pressure over the muscle bellies caused no marked increase in complaint. However, palpation of the larger nerve trunks in the extremities elicited definite tenderness.

A relative bradycardia was seen in almost every case and an absolute bradycardia in a few. This was not a prominent feature on the first or second day, but was most pronounced beginning with the third or fourth day of illness. However, any excitation of the patients seemed to cause an unusual degree of pulse rate acceleration. This lability of pulse rate persisted through convalescence.

Adenopathy was found in 54 cases or 17 per cent and was usually localized in the posterior and lateral cervical area. This finding was most pronounced after the third day of illness. The nodes were small, discrete and rarely tender. They were usually more pronounced on one side than

on the other. During this epidemic several cases were seen in various dispensaries complaining of "swelling of the side of the neck." They were otherwise asymptomatic and had no complaints. Physical examination was negative except for a unilateral enlargement of anterior cervical lymph nodes which subsided in seven to 10 days. We merely mention them as suggestive in view of their sudden occurrence in the midst of an epidemic of dengue fever.

Weakness was a major early complaint in 43 cases or 13.5 per cent, and in five cases it was the most evident early symptom. It persisted throughout the course of the illness and was the major characteristic manifested by most of the convalescents, disappearing very slowly. Mild burning of the eyes and photophobia was also an early symptom in about 5 per cent of the cases.

Dizziness, nausea and loss of taste discrimination were seen in a small number of cases and usually occurred at or just after the onset. Abdominal pain, vomiting and diarrhea or constipation were seen in a small number of cases, occurring either singly or in combination, at any time during the illness, but usually during the first half. Abdominal pain was experienced by 21 cases or 6.6 per cent and in two cases was of sufficient severity to suggest the possibility of an intra-abdominal condition. In two instances the microscopic examination of the diarrheic stools revealed the presence of many red blood cells. Efforts to relieve the existing constipation by the use of mild cathartics usually resulted in a diarrhea not commensurate with the mild medication. Insomnia was a troublesome complaint in 18 cases or 5.7 per cent but responded promptly to mild hypnotics. Upper respiratory symptoms, burning of the eyes and photophobia were met with infrequently and were very mild. Only one case had a severe intercurrent pharyngitis. Distortion or loss of taste was only partial and quite transient. It was no more marked than that experienced by many patients with a severe coryza. Cyanosis of the nail beds and cold and clammy extremities were noted in five cases or 1.6 per cent.

Examination of the blood revealed several important changes. Total white blood cell counts were done on 134 cases and in each instance showed a leukopenia. This condition quickly righted itself upon termination of the fever. The leukopenia was most pronounced on the second to the fifth day and ranged from 900 to 6700 white blood cells per cubic millimeter of blood. The average range was from 2800 to 4800 white blood cells per cubic millimeter. Differential white blood counts were done on 130 cases, and only nine cases or 6.9 per cent of this group showed a lymphocytosis of over 40 per cent. We considered this figure (40 per cent) as the upper limit of normal, since an evaluation of counts done on many individuals resident in this latitude for over six months revealed a tendency for an increase to this figure. Lymphocytosis therefore was not a constant finding in our series of cases, although two cases had a lymphocytosis of about 70 per cent. In two instances intercurrent infections caused a conversion of leukopenia to leukocytosis.

Schilling counts were done on 89 cases in this series and in each instance showed evidence of a shift to the left which started very early or perhaps prior to the onset of clinical symptoms. The "stab" or juvenile forms averaged 8 to 10 per cent on the first day of illness and 10 to 15 per cent on the third to fourth day. In many cases in which differential counts were done abnormal lymphocytes were found. They were midway in size between a large and a small lymphocyte. The nucleus was slightly eccentric and not as compact as that of the normal small lymphocyte. The cytoplasm revealed ragged areas of vacuolization which did not take the blue stain. There were many large, coarse brownish granules in the cytoplasm of these cells. These cells gave the impression of being young, hastily formed lymphocytes, or perhaps young forms with toxic granules.

A febrile albuminuria was found in 22 cases varying from one plus to two plus in extent. This was present in only one or two examinations and quickly disappeared with the drop in temperature.

The sedimentation rate was uninfluenced by the illness, and 16 cases in which it was done all gave a response within normal limits. The heterophile antibody agglutination test for acute infectious mononucleosis was carried out on 12 cases and was found within normal limits. The Kahn test for syphilis showed a negative result in all cases in which it was done. Cerebrospinal fluid examination was performed on one patient who com-

SYMPTOMS *

	Cases	Per Cent
Onset of Symptoms		
Sudden	298	93.71
Gradual	20	
Aches and Pains **	315	99.05
Headache (frontal)	219	68.86
Backache	138	43.39
Generalized Aching	112	35.22
Eyeache	80	25.15
Legache	16	
Boneache	6	
Jointache (primarily the knee)	4	
No pain	3	
Feverishness	308	96.85
Chilliness	101	31.76
Weakness (in these cases it was a prominent early symptom)	43	13.52
Abdominal Pain (severe in 2 cases)	21	6.60
Insomnia	18	5.66
Dizziness and Nausea	16	5.03
Burning of Eyes and Photophobia	15	4.74
Perversion of Taste	12	3.77
Diarrhea	10	3.14
Itching of Skin	10	3.14
Sore Throat (mild in 7 cases. Severe in 1 case)	8	2.51
Vomiting	8	2.51
Constipation	6	1.88
Numbness and Tingling of Extremities	4	1.25
Epistaxis	3	.94

* Various combinations of these symptoms were offered as complaints.

** The simultaneous occurrence of pain and aching in the various mentioned sites was frequent. This table designates the areas in order of degree of complaint.

PHYSICAL FINDINGS *

	Cases	Per Cent
Temperature Curve		
Saddle-back	210	66.03
Single rise	94	29.55
Intermittent	4	1.25
Afebrile	10	3.14
Higher in a.m.	98	30.81
Bradycardia	308	96.85
Rash	118	37.10
Site of onset		
Chest, back or abdomen (early in illness), rash later spread to extremities in 21 cases	104	88.13 (of those that had a rash)
Extremities (late in illness)	14	
Type of rash (when most pronounced)		
Macular	109	92.36 (of those that had a rash)
Maculo-Papular	3	
Scarlatiniform (rash later became petechial in 4 of these)	6	
Flushing of Skin (early in illness)	83	26.10
Face	62	
Face and chest	21	
Conjunctival Vascular Congestion	83	26.10
Adenopathy		
Total	54	16.98
Cervical	50	92.59 (of those with adenopathy)
Generalized	3	
Epitrochlear	1	
Pharyngeal Vascular Congestion	34	10.69
Hyperesthesia	20	6.28
Cyanosis	5	1.57

* Various combinations of these physical findings existed.

plained bitterly of headache and had a slight increase of pain upon flexion of the neck. This fluid revealed a cell count of 60 lymphocytes per cubic millimeter. Unfortunately this examination has not been made in any other case up to this time.

The convalescence, following the final subsidence of fever, lasted two to three and one half weeks and was more prolonged in the older patients. It was characterized by weakness, asthenia, disinclination to work, anorexia and poor appetite. During this period a moderate degree of mental depression was noted in many cases. All cases responded to symptomatic therapy and no complications occurred.

SUMMARY

Three hundred and eighteen cases of dengue fever, which occurred in army personnel during an epidemic on a South Pacific Island, were selected and analyzed as to the symptoms, physical findings and laboratory data. This island harbored numerous endemic cases of dengue fever among the civilian population, a large number of newly arrived nonimmune army personnel, and the most efficient mosquito vector, namely *Aëdes aegypti*. Those cases which occurred early in the epidemic were more atypical than the sub-

CORRELATION OF TYPE OF TEMPERATURE CURVE AND INCIDENCE OF RASH

	Saddle-back Cases	Rash	Per Cent
Incidence of rash in saddle-back type	210	77	36.66
	Non Saddle-back Cases	Rash	Per Cent
Incidence of rash in non saddle-back type	108	41	37.96
94 single rise in temperature			
10 afebrile			
4 remittent			
	Total Group	Rash	Per Cent
Incidence of rash in total group of cases	318	118	37.10

The incidence of rash was approximately the same regardless of the type of temperature curve. The incidence of rash in the total group of 318 cases was about the same percentage.

The following table lists the characteristics of our cases insofar as presence or absence of abnormal temperature curve or rash or both, in order of frequency of occurrence.

	Cases	Per Cent
Saddle-back temperature curve and no rash	133	41.82
Saddle-back temperature curve and rash	77	24.21
No saddle-back temperature curve and no rash	67*	21.06
No saddle-back temperature curve and rash	41	12.89
	318	

* This relatively large group had sufficient other evidences of the illness to warrant inclusion, such as severe frontal headache, backache, weakness and leukopenia. Most of this group were ill in the early phase of the epidemic.

LABORATORY FINDINGS

	Cases	Per Cent
Leukopenia (134 white cell counts done)	134	100
Lymphocytosis (130 differential counts done)	9 (over 40%)	6.92
Schilling Shift to Left (89 Schilling counts done)	89	100
Abnormal Lymphocytes	Present (described in text)	
Albuminuria (292 urinalyses done)	22 (one plus to two plus)	7.53

Sedimentation Rate (done on 16 cases and within normal limits in all)
Heterophile Agglutinations (done on 12 cases and within normal limits in all)
Kahn (negative in all cases)
Cerebro-spinal Fluid Count (done on 1 case) 60 lymphocytes per cubic millimeter.

sequent cases and, therefore, caused some difficulty in correct diagnosis. The onset of symptoms occurred suddenly in about 93 per cent of the cases after an incubation period of six to 10 days. Ninety-nine per cent had aches and pains in one or more sites. The frontal headache, backache, and generalized aches and pains were common complaints. Feverishness and chilliness were frequent and early symptoms. Weakness, abdominal pain and insomnia occurred next in order of frequency. Dizziness, nausea, burning of the eyes, photophobia and distortion of taste were complained of in a small number of cases. Diarrhea, itching of skin, sore throat, vomiting, constipation, numbness and tingling of extremities and epistaxis were last in order of frequency.

The temperature curve was saddle-back in about 66 per cent of cases and non-saddle-back in about 33 per cent. A relative bradycardia was found after the second day of illness in 97 per cent of cases. A rash was present

in 37 per cent of all cases. The initial site of involvement was the chest, back or abdomen in about 88 per cent of those who manifested this physical finding. The most common type of rash was a widespread, blotchy, macular erythema. In rare instances it was maculopapular, scarlatiniform or petechial. A diffuse flushing of the skin, primarily of the face or face and chest was seen in about 26 per cent of cases. A marked reddening of the ocular conjunctiva was seen early in the illness in about 26 per cent of the individuals involved. Adenopathy, mostly cervical, was seen in about 17 per cent. Pharyngeal vascular congestion was found in 11 per cent of cases. Hyperesthesia, although it was uncommon and occurred only in 6 per cent, was rather severe. Cyanosis of the fingers and toes was found in about 1.6 per cent of cases.

Examination of the laboratory data revealed that all cases had a leukopenia and a Schilling shift to the left. A lymphocytosis of over 40 per cent occurred in about 7 per cent. Abnormal lymphocytes with a vacuolated cytoplasm and coarse granular inclusions were a rather constant finding. A febrile albuminuria was present in about 8 per cent of cases.

The convalescence was moderately prolonged. However, all cases responded to symptomatic therapy and there were no complications.

The authors wish to express their appreciation to Major General Robert G. Breene and to Colonel Earl Maxwell, M.C., whose invaluable coöperation and advice were instrumental in the formulation of this paper.

Appreciation is also rendered to Captain Rhett G. Harris, Sn. C., and Technical Sergeant Lawrence A. Hull for technical assistance.

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FURTHER STUDIES OF PLATELET REDUCING SUBSTANCES IN SPLENIC EXTRACTS *

By EUGENE P. CRONKITE, M.D., *San Francisco, California*

TROLAND and Lee, in 1938,[1, 2] reported that acetone extracts of spleens from patients with "idiopathic" thrombopenic purpura produced a marked transient lowering of platelets when injected into rabbits. Some subsequent workers confirmed these results; others were unable to reproduce them.[3, 4] Rose and Boyer,[5] however, reported in 1940 from this clinic definite platelet lowering effects of spleen extracts from purpura cases and concluded that the results of Troland and Lee must be accepted. In 1940 Paul [6] again reviewed the literature and made further experiments demonstrating a platelet depressing substance.

The present report deals with further studies of the effect of splenic extracts in lowering the platelet count of rabbits, but new types of material were used including some from a patient with thrombopenic purpura associated with miliary tuberculosis of the spleen and some from a child with chronic severe neutropenia without thrombocytopenia.

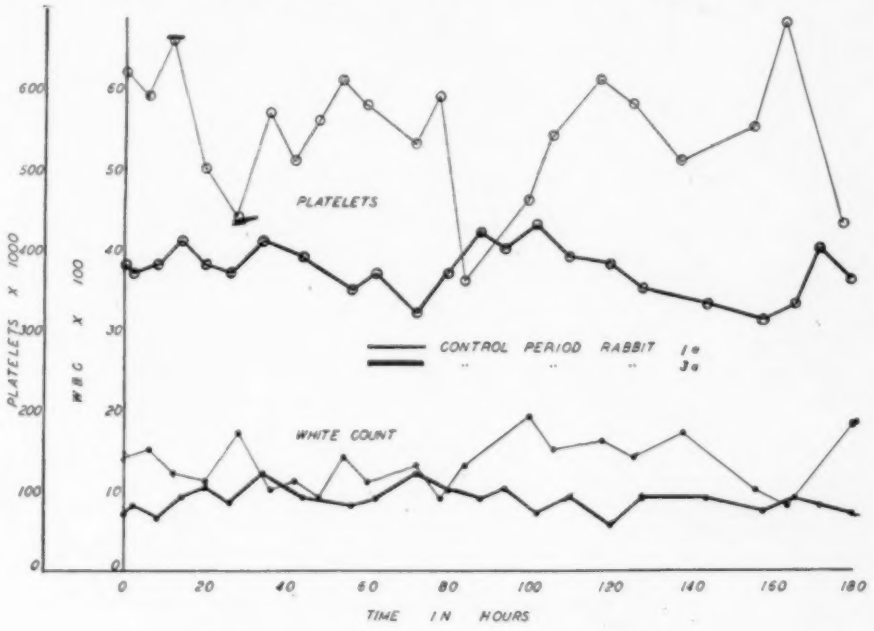
METHODS

Immediately after removal the spleens were ground up and extracted in a refrigerator with five times their weight of acetone. The supernatant fluid was evaporated to constant volume by suction at room temperature and the brown gummy residue was diluted to 100 c.c. with distilled water, filtered through a Seitz filter into vaccine bottles, and stored in a refrigerator at 10° C. This material was injected into unselected, young, male rabbits in the amounts stated on the charts. Platelet and other counts were made at from three to six hour intervals to determine a base line before the injections, and again until the counts returned to the original levels. Platelet counts were done by the method of Rees and Ecker as described in Todd and Sanford's textbook.[7] Details of technic may be found in the previous report of Rose and Boyer.[5] Bleeding time was determined by a puncture of the marginal ear vein, with needles of the same diameter, after shaving and cleaning with ether. Bleeding times are recorded on the charts. Capillary fragility was determined on the shaven abdomen by the method of Dalldorff.[7] Clot retraction was determined by removing blood by cardiac puncture and placing two cubic centimeters in a chemically clean tube under light mineral oil.

* Received for publication August 18, 1942.

From the Department of Medicine, Stanford University School of Medicine, San Francisco, California.

Normal Variations in the Platelet Counts of Rabbits. In order to determine the average count of rabbits and to see how great and rapid the swings might be, counts were made on the average of three times per day for one week before beginning any of the experimental work (chart 1).



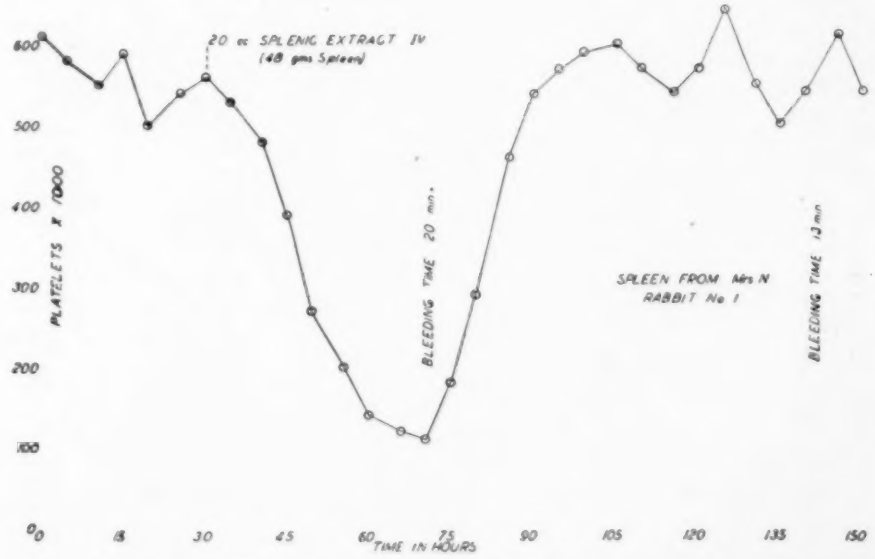
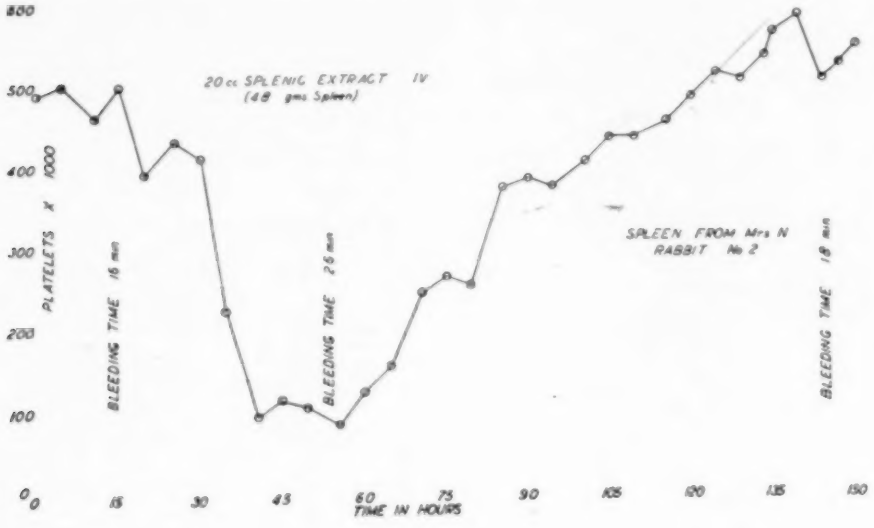


CHART 1. (*Above*) Variations in platelet and leukocyte counts in normal control rabbits.

CHART 2. (*Below*) Platelet depressing effect of splenic extract from case of "idiopathic" thrombopenic purpura. (Case 1.)

It is apparent that there is normally a rather large swing from hour to hour and from day to day. From this chart and from the initial counts done on other rabbits, one can postulate, therefore, that the normal level of platelets for this group of animals is from 200,000 per cu. mm. to 700,000 per cu. mm.



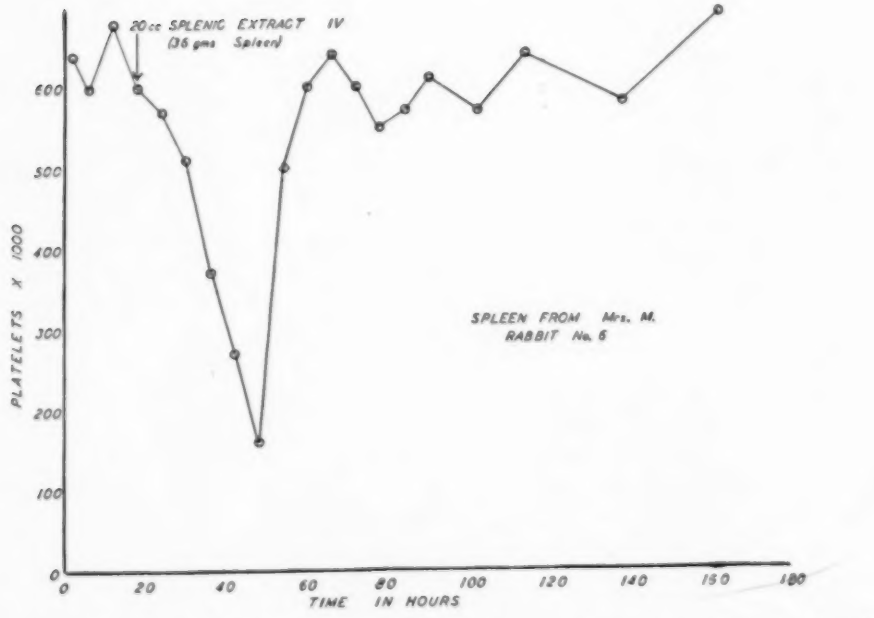


CHART 3. (*Above*) Platelet depressing effect of splenic extract from case of "idiopathic" thrombopenic purpura. (Case 1.)
CHART 4. (*Below*) Platelet depressing effect of splenic extract from case of "idiopathic" thrombopenic purpura. (Case 2.)

However, a difference of 500,000 has not been observed on successive counts in any one animal under normal conditions. The largest normal variation observed in one animal was 300,000 per cu. mm. Therefore, it is difficult to set up any standard limits which must be exceeded in order to indicate the presence of a factor affecting platelet levels. On the contrary, one must determine the control level for each animal, and then judge the results upon their own merit in each experiment.

Experiments

Case 1. "Idiopathic" Thrombopenic Purpura. Mrs. M. L. N., 26, American, housewife, entered Stanford Hospital on January 22, 1941, complaining of a tendency to bleed and to bruise since early childhood. There was no familial history of similar disease. No toxic factors were discovered and her diet had been adequate in vitamins. A tonsillectomy in July 1940, was followed by prolonged hemorrhage. The patient had suffered from innumerable nosebleeds in childhood, severe bruising on slight trauma, and menorrhagia lasting over seven days.

Physical examination revealed a young woman in good general condition with petechiae on gums, tongue and skin. Fundi clear. Liver and spleen not felt. No adenopathy. Lungs clear.

Essential laboratory data: Red blood cells 6.0 million; hemoglobin 76 per cent Sahli; color index 0.6; white blood cells 7,200—normal differential; platelets 18,000; bleeding time 15 minutes (Duke); clotting time 4.5 minutes (Lee-White); clot retraction, none after 24 hrs. fragile; capillary fragility, 2 petechiae per cm.^{2} at 20 cm. Hg; negative pressure; positive tourniquet test with blood pressure cuff at 40 mg. Hg for 3 minutes.

Splenectomy was performed on January 28, 1941, following which platelets rose progressively to 809,000 on the third postoperative day. Five hours postoperatively the bleeding time was normal and the clot began to retract. Since dismissal the platelets have fallen, but have never been below 164,000 per cu. mm.

Extract equivalent to approximately 50 gm. of spleen was injected into two rabbits. Forty hours after injection of the first animal (chart 2) the count had dropped from 560,000 to 110,000 per cu. mm., a drop of 450,000 which greatly exceeded the maximum swing of 100,000 during the control period. Sixty hours after injection the count had returned to normal. Bleeding time was not determined initially in this animal but was over 20 minutes when the platelet count was down to 110,000. Later it fell to 13 minutes. The second rabbit (chart 3) showed a similar response of even greater magnitude, and the changes in bleeding time, clot retraction and capillary fragility were as follows:

	Bleeding Time	Clot Retraction	Capillary Fragility
Initial	16 min.	Started in 2 hrs. Complete in 11 hrs. Firm and rubbery	0 petechiae per sq. cm. at − 20 cm. Hg.
At maximum platelet drop	26 min.	Started in 6 hrs. Complete in 18 hrs. Clot breaks easily	4 petechiae per sq. cm. at − 20 cm. Hg. 0 petechiae per sq. cm. at − 10 cm. Hg.
After return to normal	18 min.	Started in 6 hrs. Complete in 14 hrs. Firm clot	0 petechiae per sq. cm. at − 20 cm. Hg.

Summary: Extract of spleen from a case of long standing "idiopathic" thrombopenic purpura produced definite lowering of platelets similar to that described in other cases by Rose and Boyer.

Case 2. "Idiopathic" Thrombopenic Purpura. Mrs. M., 39, Italian, housewife, entered Stanford Hospital complaining of bruising and bleeding easily during her entire life. There was no history of any toxic agent which seemed responsible for her hemorrhagic diathesis. The illness dated back to childhood and was characterized by profuse bleeding from minor wounds, severe bruising without provocation, epistaxis and menorrhagia. Transfusions, local thromboplastin, liver therapy, etc., had been of little value and the patient entered for splenectomy.

Physical examination showed a young woman with showers of petechiae and purpuric blotches on the skin and mucous membranes. Fundi were clear. There were splinter hemorrhages under the nails. The liver and spleen were not felt. There was no adenopathy. The lungs were clear.

Essential laboratory data: Red blood cells 4.07 million; hemoglobin 92 per cent Sahli; white blood cells 8,800, normal differential except 8 per cent eosinophiles; platelets 8,000 to 12,000 per cu. mm.; bleeding time 18 minutes; clot retraction, fragile clot with none after 24 hours; clotting time 2.5 minutes (Lee-White); capillary fragility, showers of petechiae in 1 cm.^{2} at 20 cm. Hg negative pressure. Peck-Rosenthal positive. Bone marrow aspiration showed an occasional megakaryocyte and an increase of eosinophiles.

Splenectomy was performed on September 11, 1941, following which a striking elevation of platelets occurred, attaining 2,540,000 on the third postoperative day. The patient was well and active three weeks later despite a low platelet count of 21,000, and has remained well.

Extract equivalent to approximately 35 grams of spleen was injected intravenously into rabbit No. 6. A similar platelet response to that in case 1 (see chart 4) was obtained but was of lesser magnitude. No definite changes were noted in bleeding time, clot retraction and capillary fragility.

Summary: The results in this case also confirm the presence of a platelet lowering factor in acetone extracts of spleen from "essential" thrombopenic purpura.

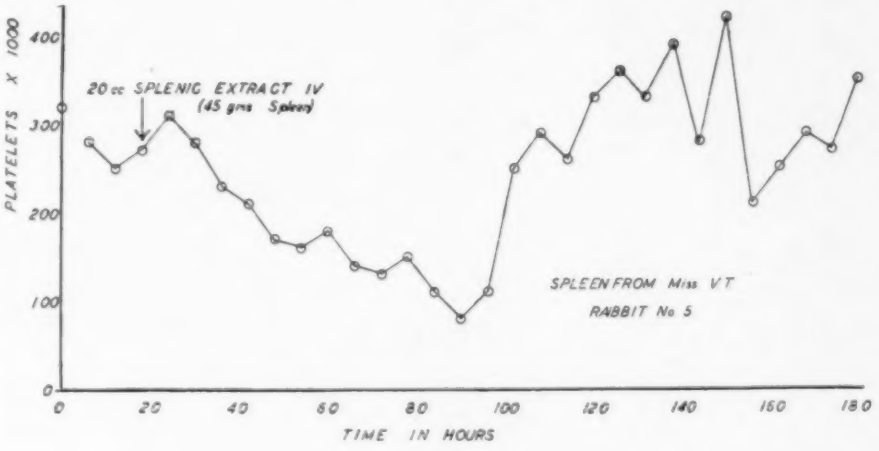
Case 3. Thrombopenic Purpura Associated with Tuberculosis of Spleen. V. T., aged 19, a white American waitress, had all the usual findings of "idiopathic" thrombopenic purpura. On splenectomy, however, the spleen showed many small tubercles containing acid fast bacilli. There was no immediate platelet response after removal of the spleen, although the patient eventually recovered. The case will be reported in detail elsewhere.

Spleen extract derived from 45 grams of material was injected into each of two rabbits. Response in the first of these animals (chart 5) was not striking. Seventy hours after injection the count had fallen from an initial value of 270,000 to 90,000 per cu. mm. In 85 hours the count was back to normal ranges. In the second rabbit (chart 6) the count at first increased from 460,000 to 740,000 per cu. mm. and then fell to 200,000 sixty-eight hours after injection. No changes were demonstrated in bleeding time, clot retraction, or capillary fragility in either animal.

Summary: The results seem equivocal in this case; certainly there is no convincing evidence of a platelet lowering substance, at least of the potency found in the cases of "idiopathic" thrombopenia. Superficially one might think that a definite depression had occurred, but when one refers back to the

pre-injection levels and considers the normal variations in rabbits, the magnitude in this experiment is not convincing.

Case 4. Chronic Malignant Neutropenia. H., a seven year old girl, had a family history of low granulocyte counts and of an absolute lymphocytosis in the mother and



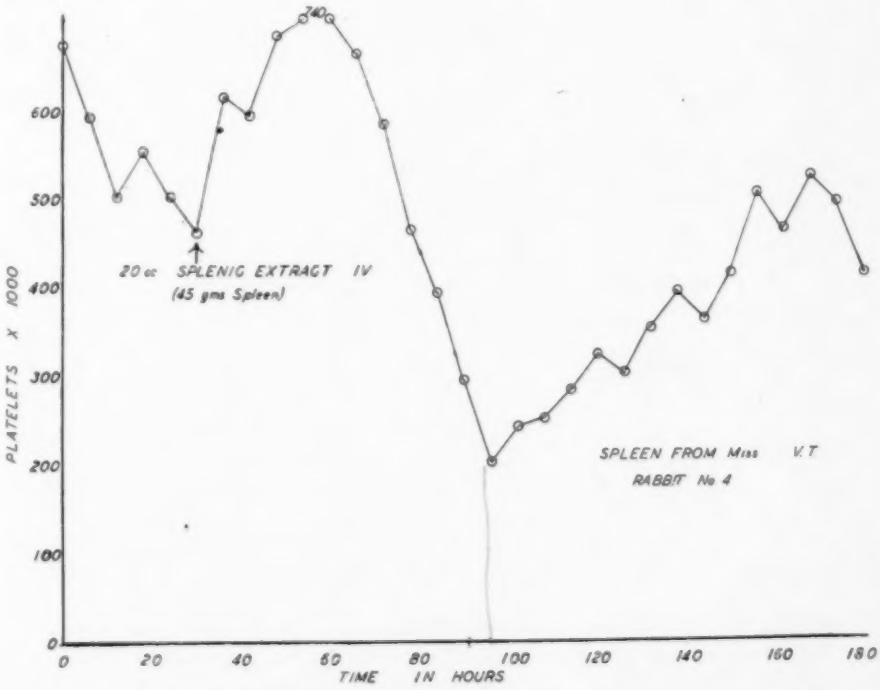
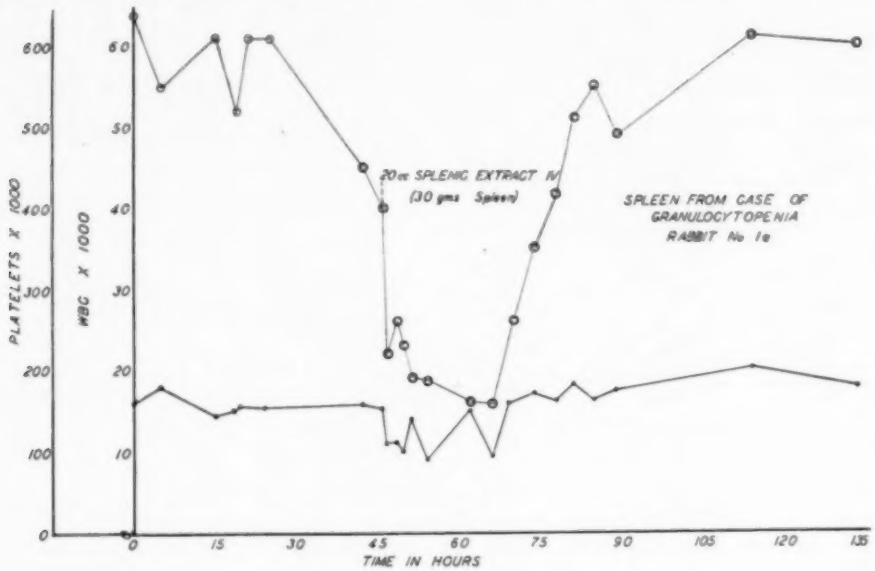


CHART 5. (*Above*) Platelet counts following injection of splenic extract from Case 3 (tuberculosis of spleen).

CHART 6. (*Below*) Platelet counts following injection of splenic extract from Case 3 (tuberculosis of spleen).

brother. There was no history of ingestion of any drug or poison. Her hospital course was stormy, with gingivitis, stomatitis, pustular dermatitis, jaundice, hepatomegaly and irregular fever. Her white count showed a high total cell count with marked granulocytopenia, lymphocytosis, monocytosis and thrombocytosis. A typical



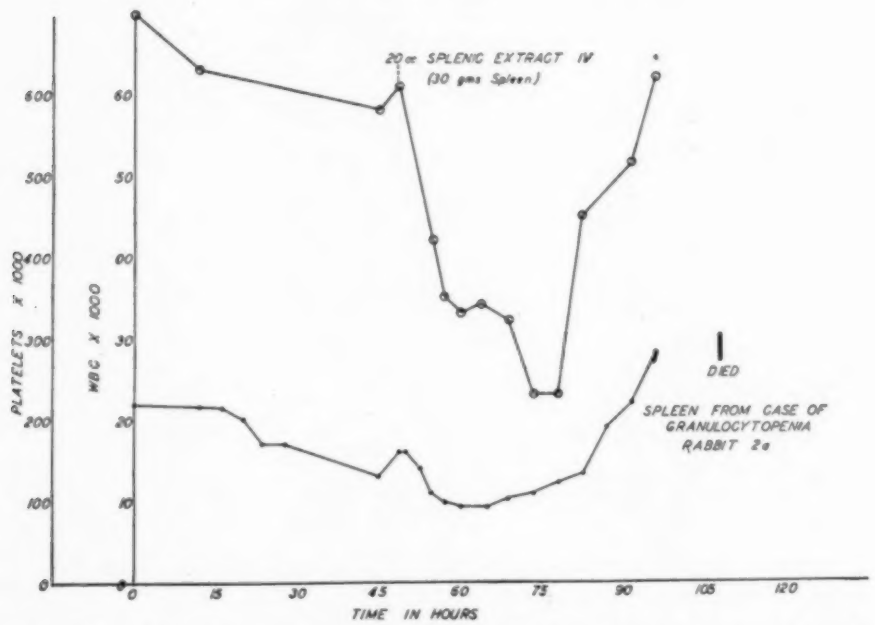
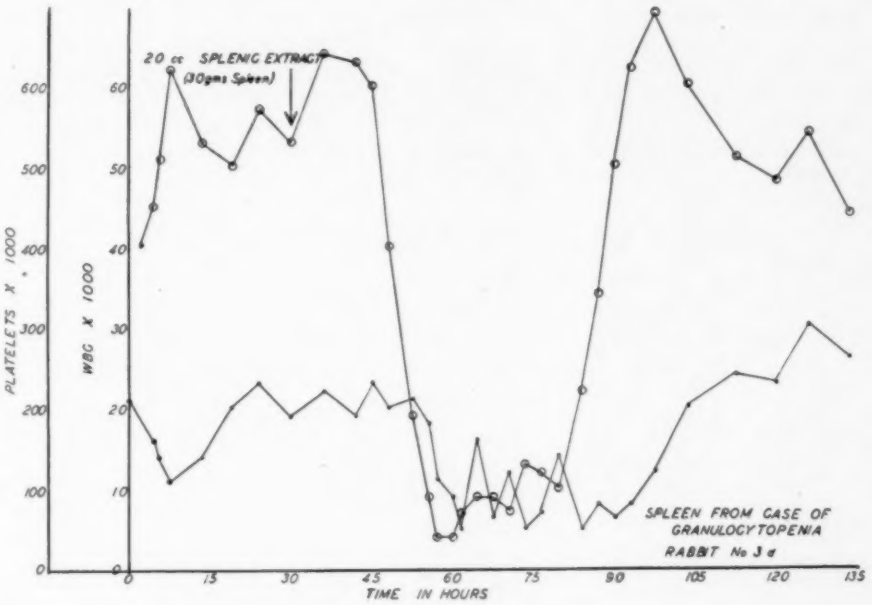


CHART 7. (*Above*) Platelet depressing effect of splenic extract from case of chronic "malignant" neutropenia.

CHART 8. (*Below*) Platelet depressing effect of splenic extract from case of chronic "malignant" neutropenia.

count was as follows: Red blood cells 6.5 million; hemoglobin 115 per cent Sahli; reticulocytes 0.5 per cent; platelets 885,000 per cu. mm.; white blood cells 14,700; neutrophiles, segmented 1 per cent, banded 1 per cent; lymphocytes 49 per cent; monocytes 47 per cent; eosinophiles 1 per cent.



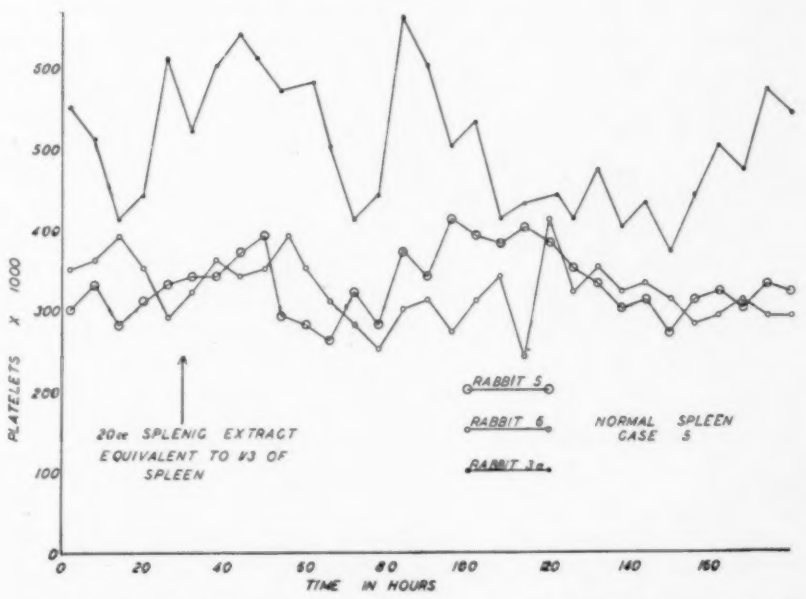


CHART 9. (*Above*) Platelet depressing effect of splenic extract from case of chronic "malignant" neutropenia.

CHART 10. (*Below*) Platelet counts following injection of splenic extract from normal control.

Leukemia was ruled out as far as possible. There was no response to transfusion and finally splenectomy was performed, following which there was no immediate change.*

Extract equivalent to 30 gm. of spleen was injected into each of three rabbits. In rabbit la (chart 7) there was a fall of platelets from 400,000 to 160,000 per cu. mm. within 20 hours, with return to normal 30 hours after injection. In rabbit 2a (chart 8) similar results were obtained but the animal died of pneumonia.

In rabbit 3a (chart 9) the greatest depressions of platelets occurred. For 15 hours following injection there was a brief elevation of 110,000 to 640,000 per cu. mm. and then a profound fall in 20 hours to 40,000. The depression was maintained longer than in any other experiment, and the platelets did not return to normal until 65 hours after injection. There were no significant changes in the white cell counts (see charts 7, 8, and 9).

The following table gives the changes in bleeding time, clot retraction, and capillary fragility:

Animal	Time Taken	Bleeding Time (minutes)	Clot Retraction	Capillary Fragility (Petechiae per sq. cm.)
1-a	Initial	12	Started in 30 min. Complete in 4 hrs. Clot firm	None at 20 cm. Hg
	Maximum platelet depression	> 25	Started in 2 hrs. Complete in 8 hrs. Clot softer	8 at 20 cm. Hg None at 10 cm. Hg
	After return to normal	15	Started in 1 hr. Complete in 10 hrs. Clot firm	None at 20 cm. Hg
2-a	Initial	10	Started in 1 hr. Complete in 4 hrs. Clot firm	None at 20 cm. Hg
	Maximum platelet depression	15	Started in 1 hr. Complete in 8 hrs. Clot firm	None at 5 cm. Hg 12 at 10 cm. Hg 16 at 20 cm. Hg
	Animal died			
3-a	Initial	6	Started in 15 min. Complete in 5 hrs. Clot firm	None at 20 cm. Hg
	Maximum platelet depression	> 30	Started in 15 hrs. Complete in 11 hrs. Clot same	None at 5 cm. Hg 6 at 10 cm. Hg 30 + at 20 cm. Hg
	After return to normal	8	Started in 30 min. Complete in 12 hrs. Clot same	None at 20 cm. Hg

Summary: A strong platelet depressing factor was present in the spleen from this case of neutropenia, although the patient showed thrombocytosis rather than thrombopenia.

* We are indebted to Dr. H. K. Faber for permission to refer to this case which will be reported in full from the Department of Pediatrics.

Case 5. Normal Control. An 11 year old boy fell, injuring his spleen, which was removed 20 hours after the accident. The boy was normal in every respect.

Extract equivalent to about 33 gm. of spleen was injected into each of three rabbits (chart 10). There were no significant changes in platelets, bleeding time, clot retraction or capillary fragility.

Discussion

The presence of a platelet depressing factor in acetone extracts of spleens from "idiopathic" thrombopenic purpura has been repeatedly affirmed and denied by various workers. The reason for the discrepancy is not clear, but many factors are to be considered.

First, Troland and Lee demonstrated that the potency of the extract diminished with heating. Perhaps other factors such as oxygen, the presence of some metal as a catalyst, or other minor chance happenings have acted to inactivate "thrombocytopen." Further work should be done along these lines, controlling all phases of the extraction as would be done in searching for an enzyme or hormone.

Second, the normal platelet counts of rabbits have not been considered to a great enough extent. Perhaps some of the positive results, such as those of Paul, should be considered as not definitely confirmatory.

Third, "thrombocytopen," when demonstrated, has been considered as a specific substance occurring in spleens of cases of idiopathic thrombopenic purpura. "Thrombocytopen" has not been demonstrated in normal spleens or spleens from leukemias, Banti's syndrome, aplastic anemia, congenital hemolytic jaundice and splenic vein thrombosis (Rose and Boyer, and Paul). However, the present work demonstrates what appears to be an even more potent platelet depressing factor from idiopathic malignant neutropenia with thrombocytosis. Indefinite responses were obtained from a case clinically resembling idiopathic purpura, but whose spleen was tuberculous.

In summary, then, there is no doubt of the crude fact that platelet lowering substances may be extracted from certain spleens. Since this has now been established beyond question there will be little point in further repetition of this work by the same methods. The next step must be in the hands of chemists qualified further to purify and identify the effective substances.

Summary

1. Troland and Lee's demonstration of "thrombocytopen" has again been confirmed at this clinic in cases of "idiopathic" thrombopenic purpura.

2. An identical action has been demonstrated in similar acetone extracts of a spleen from chronic malignant neutropenia.

3. It is suggested that the platelet reducing factor may not be specific for idiopathic thrombopenic purpura.

4. The great variability of platelet counts in the same and in different rabbits has been demonstrated.

5. Evidence suggestive of changes in bleeding time, clot retraction and capillary fragility following intravenous injection of these extracts is offered. This should be investigated more fully.

6. Further work should be done along more accurate chemical lines in isolating and determining the nature of this substance.

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OSTEO-NEPHROPATHY: A CLINICAL CONSIDERATION OF "RENAL RICKETS"*

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The association of bone changes and renal disease has long been recognized,[1] and for some years these associated phenomena have been designated as "renal rickets." Within the past decade, however, the plurality of the underlying disorders responsible for this clinical syndrome has been established. There is evidence that some patients suffering from the condition may be dramatically improved with appropriate therapy,[2] whereas treatment of the more outstanding manifestations of the disease may be followed by aggravation of the symptoms. An attempt to set up criteria for the differentiation of the various forms of the disorder is therefore indicated. Two cases are added to the literature, one illustrating a satisfying response to therapy.

The term "renal rickets" should be discarded; it has included conditions which were not primarily renal and were not rickets (reserving the term "rickets" for the deficiency disease due to avitaminosis D). Its continued use tends to foster a misunderstanding of the underlying pathologic mechanisms. We have adopted the term osteo-nephropathy, since it indicates the nature of the presenting symptoms without implication regarding pathogenesis, as in the term "renal rickets."

Table I

An Etiological Classification of Osteo-Nephropathy

A. Due to primary urinary tract disturbances
1. Chronic glomerulonephritis, pyelonephritis, nephrosis
2. Congenital malformations: Polycystic kidneys, renal hypogenesis
3. Urinary tract obstruction with secondary renal lesions: Urethral valves; prostatic enlargement; calculi; strictures of urethra, bladder neck or ureter; hydro-ureter
4. Primary tubular functional changes which may or may not show anatomical changes.
   a. Hypochloremic-glycosuric type (deToni-Fanconi syndrome)
   b. Hyperchloremic type without glycosuria

B. Due to primary extra-renal disturbances
1. Endocrine disease
   Hyperparathyroidism (osteitis fibrosa cystica)
2. Metabolic disturbance
   Cystine storage disease

In table 1 is given an etiologic classification, in the light of our present knowledge, of the various forms of osteo-nephropathy. It will be seen that in the analysis of any case of associated bone and renal disease, two main possibilities must be considered, the type in which the kidney (or genito-

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urinary tract) is primarily involved and the type in which the primary process is extrarenal in origin. It is important to note that even in cases in which the condition is due to primary renal disease, the kidneys will not always show marked alteration of structure when studied post mortem. This is due to the fact that disturbances of tubular function (for example, that due to phloridzin poisoning, adrenal cortical insufficiency, or lesions of the posterior pituitary) may be present without evidence of anatomical change, as noted by the usual methods of pathological examination.

General Considerations. The symptoms of this group of diseases depend on the fundamental nature of the disorder and on the extent and duration of the renal damage. The type and degree of the bone changes show extreme variation and, in addition to determining the fundamental disorder, their evaluation must take into consideration the age of onset, the rate of bone growth, and the duration of the condition. If the onset of the condition is late and the underlying disease mild, the skeletal deformity may be slight. In most instances the bones show generalized osteoporosis, deformities (genu valgum or varum, Harrison's groove, rickety rosary, pigeon breast) and dwarfism.[3]

Renal disturbances account for the commonly observed symptoms of nocturia, polyuria and polydipsia, for the signs of acidosis, for the terminal picture of uremia and possibly for the color changes in the skin. The features of generalized malnutrition, retarded sexual and mental development, and the types of intercurrent infection are variable and non-specific in nature.

Accessory Clinical Studies. The determination of the nature of the disorder rests ultimately on the accessory clinical studies, especially upon the chemical studies of the blood and urine. The roentgenogram in some cases may indicate the fundamental disorder by showing bone cysts characteristic of primary hyperparathyroidism, calcification in the kidney, or other changes in the genitourinary tract. Further, repeated roentgenograms aid in the evaluation of therapy.

The bone picture usually resembles that seen in experimentally induced, so-called "low calcium-high phorphorus rickets." In advanced stages of the disease there is a greater translucency of the shafts of the long bones and flat bones and a more porous appearance than in rickets; multiple healed fractures may be present. However, the roentgenogram, even in the hands of the expert, is not definite except in hyperparathyroidism.

Since the differentiation of the various types of osteo-nephropathy often depends on the laboratory studies, these are summarized in table 2. Cystine storage disease is not included; its diagnosis depends upon the demonstration of cystine crystals in the urine or deposited in the tissues.[4]

As in the case of the roentgenogram the other accessory findings vary with the extent and duration of the disease. Although anemia and the urinary findings of fixed specific gravity, albumin, red and white blood cells and casts are prominent in the cases in which there is marked anatomical change in the kidney, i.e., in chronic glomerulonephritis, malformations,

and urinary tract obstruction, these may be found in the late stages of any form of osteo-nephropathy.

Primary Renal Disease with Well-Recognized Anatomical Changes. This group includes the conditions listed as 1, 2, and 3 under A of table 1. These are cases which lead, both in the child and the adult, to renal failure with nitrogen retention and death in uremia. The vast majority of the cases of osteo-nephropathy recorded in the literature fall into this group and comprise mainly those secondary to chronic glomerulonephritis.[5]

TABLE II

Chemical Findings in the Blood and Urine in Osteo-Nephropathy

	Primary Renal Disease			Hyperparathyroidism (Juvenile osteitis fibrosa cystica)
	a. Chronic glomerulo-nephritis *b.* Malformations *c.* Urinary tract obstruction	Tubular Dysfunction		
		Hypochloremic-glycosuric type	Hyperchloremic type	
Serum calcium	Normal or slightly reduced	Reduced	Reduced	Elevated
Blood phosphate (inorganic)	Elevated	Reduced	Reduced	Reduced
Blood non-protein nitrogen	Elevated	Normal or slightly elevated	Normal or slightly elevated	Normal
Carbon dioxide combining power of blood	Normal or slightly reduced	Reduced	Reduced	Normal
Serum chlorides	Normal	Reduced	Elevated	Normal
Organic acids of blood	Normal	Elevated	Normal	Normal
Glycosuria	Absent	Present	Absent	Absent
Ketonuria	Absent	Present	Absent	Absent
Anemia	Usually marked	Usually slight	Usually slight	Usually slight

A suggested mechanism for the bone changes observed in this group[6] is that, concomitant with renal failure and nitrogen retention, phosphate excretion through the kidneys is reduced. Phosphate is excreted into the gut with calcium or produces a precipitate with the calcium of the diet within the intestinal lumen, thereby interfering with absorption of the latter. It is well known also that phosphate retention leads to parathyroid hypertrophy,[7] and the bone changes have been attributed as secondary to this. This theory is unlikely.[8] The rôle of acidosis is important[9] and the necessity of additional factors has been postulated to account for the inconsistency of the bone changes and the extent of the renal damage.

The age at which clinical symptoms bring these patients to the physician may vary from infancy until the age of 10.[5] Even when the condition is secondary to a congenital lesion, infancy may be passed before the patient is seen, since the renal failure may not be striking at an early age. Prognosis depends on the extent of the underlying kidney damage. About one-

half of the reported cases were alive at 10 years, but only a few survived to the age of 20.[8]

Treatment in the main should be directed to the underlying renal disease with special emphasis on urologic aid in cases secondary to urinary tract obstruction. Some success [9] is reported with the use of alkali therapy (15 grams of sodium bicarbonate daily) adjusting the dose by the carbon dioxide combining power of the blood. Vitamin D in daily doses of 20 or 30 thousand units may result in some healing. Since tetany can be precipitated with alkali or phosphate administration (by reduction of the ionized calcium) calcium administration is also indicated. Ultraviolet irradiation is said to aggravate the condition.[10] The anemia should be corrected by such measures (transfusions, iron, liver) as are indicated.

Tubular Dysfunction. In this group we have included those patients in whom the renal insufficiency is a result of a disturbance in tubular function. The commonly observed disturbances of the kidney involve alterations in the structure of the nephron, which are evident post mortem. However, the major work of the kidney is performed by the tubular cells the functional integrity of which is essential if the glomerular filtrate is to be prevented from reëntering the circulation. It is such a tubular dysfunction (not demonstrable by the usual procedures of pathological anatomy) which is present, for example, in phloridzin poisoning and in adrenal cortical or posterior hypophyseal insufficiency,[8] and which is responsible for the renal disturbance present in these conditions. A similar tubular dysfunction is responsible for a group of patients suffering from osteo-nephropathy. Clinically, this group may be subdivided into two categories differentiated by the presence in one of a normal or reduced blood chloride and glycosuria, and in the other of an hyperchloremia without glycosuria.

The Hypochloremic-Glycosuric Type. Less than a dozen cases [12, 13, 14, 15, 16] which fit into this group have been reported since the original descriptions by deToni [10] and Fanconi.[11] All of the reports have concerned individuals under five years of age with the majority in infancy. The reported consanguinity in the parents [11] and the occurrence of more than one case in the same family [16] point to a congenital basis for the disorder. The presenting symptoms include, in addition to the growth and developmental deficiency, marked anorexia, polyuria, and incidental respiratory and urinary tract infections. Roentgenographic changes, rickets-like in appearance, are non-specific. As noted in table 2, diagnosis is confirmed by the finding of a low calcium and inorganic phosphate in the blood, glycosuria, acidosis and a tendency toward hypochloremia. The urine is frequently alkaline in reaction in spite of the marked systemic acidosis as shown by the symptoms, the low carbon-dioxide combining power of the blood and the presence of an elevated organic acid level in the blood. The urine usually reveals a relatively fixed specific gravity (when corrected for the presence of albumin and sugar), moderate amounts of albumin, casts, red and white blood cells and

greatly increased amounts of inorganic phosphate, ammonia and organic (amino and lactic) acids.[11, 14] The glycosuria appears to be of the renal type, since it occurs with low or normal blood sugar levels. An abnormality in carbohydrate metabolism is shown by a wide variation in the fasting blood glucose tolerance curve. The latter shows high peaks, as in the diabetic, but starts at normal or subnormal levels. There is also a marked secondary rise after the administration of epinephrine. Neither the glucose tolerance nor the response to epinephrine injection should be studied on these patients since such studies have been followed by severe reactions and death in two instances.[11] Electrocardiograms may show changes from the normal but these are of no aid in the diagnosis.

A lability of the body temperature has been striking; it has fluctuated from normal to both hypo- and hyperthermic levels in the absence of any infection. The glycosuria may disappear temporarily and modest improvement in the general symptoms and in the appearance of the bones may take place. However, all but a few of the reported cases have died before the age of seven, acidosis and renal failure with convulsions characterizing the terminal picture.

The autopsy findings of vacuolization and degenerative changes in the renal tubules,[11, 16] the absence of striking glomerular changes and particularly the chemical findings in the blood and urine point to the kidney tubule as the site of the fundamental disorder. The loss of concentrating power, the renal glycosuria and albuminuria support this assumption. The existence of a tubular dysfunction also best explains the disturbance in the acid-base balance. The urine, as mentioned, is alkaline or only slightly acid even in the presence of systemic acidosis. This impaired capacity of the kidney to secrete acid seems to be partially compensated for by (1) an increase in the volume of the urine with a diminished loss of fluid through other channels (the bowel, the skin, etc.), (2) an increased excretion of buffer substances, especially phosphates which are found in the urine in large amounts, and (3) by an increase in the ammonia content of the urine. The bone changes are explained as secondary to the chronic acidosis and low concentration of the calcium and inorganic phosphate of the blood.

The possible rôle of the liver in the production of this condition has not been evaluated: The occurrence of jaundice and a palpably enlarged liver, the high amino and other organic-acid content of the blood, the abnormalities of carbohydrate metabolism and the lability of the body temperature suggest the involvement of some hepatic factor. There is no good evidence to implicate any endocrine organ in the pathogenesis of the disorder.[8]

Therapy in these cases has been disappointing. Some improvement has been reported [14] following the use of a high potassium, low sodium diet. The deficiency in calcium and phosphorus should be counteracted by the administration of dicalcium phosphate and large doses (20,000 to 30,000 U.S.P. units daily) of vitamin D. In spite of the apparent logic of these procedures, attempts to correct the acidosis with sodium citrate-citric acid buffer and

sodium bicarbonate have not been impressive,[15] but further trials will be necessary before definite conclusions may be drawn.

Hyperchloremic Type. Information relative to this variety of tubular dysfunction is limited to six examples cited in the literature [2, 17] in addition to the case which is presented in the present article. Several features differentiate it from the entity previously described, and the evidence of its dramatic response to therapy in some cases makes its recognition important. These features are (1) the presence of diffuse calcification of the renal tubules, (2) the absence of glycosuria, and (3) the presence of an acidosis associated with an elevated blood chloride level. These cases do not show the increase in the organic acid content of the blood and urine observed in the hypochloremic-glycosuric type.

The onset of the disorder is usually early in life, four cases having been reported in infants.[17] The chemical findings and the calcification of the renal tubules in addition to the severe acidosis which resisted attempts at correction justify their inclusion in this group. Death of all these patients occurred before the age of one year, and the absence of rickets-like bone changes may possibly be explained by the acute course in two of the cases and the degree of starvation in the others.

The following has been suggested as the mechanism responsible for the observed bone changes.[2] Inability of the kidney to manufacture ammonia or to secrete an acid urine leads to a shortage of base with which to excrete mineral acids, particularly chloride. The resulting acidosis is followed by a low serum calcium and a low inorganic blood phosphate, which in turn induce hyperplasia of the parathyroid glands, and "low phosphorus rickets."

The therapy that has proved successful in the patient to be described later and in the other reported case [2] consists of (1) a low salt diet, (2) six grams of di-basic calcium phosphate daily in divided doses with milk, (3) 20,000 units daily of vitamin D, and (4) 30 cubic centimeters of a sodium citrate and citric acid buffer mixture three times daily, one half hour before meals. This citric acid and sodium citrate buffer mixture is two-thirds molar in respect to citric acid and one-third molar in respect to sodium citrate; it is made by dissolving 140 grams of citric acid and 98 grams of sodium citrate in water to a volume of one liter.[21]

The above régime was devised as a result of metabolic studies [2] which indicated that administration of salt was followed by an increase in the acidosis, whereas a salt-free diet decreased it. The administration of the sodium citrate and citric acid buffer mixture not only reduces the acidosis, but also causes an increase in calcium retention. The administration of calcium phosphate, the absorption of which is aided by the added vitamin D, acts to overcome the deficiency of these minerals and to increase available base. A dramatic response to this therapy has been reported [2] and is shown in our patient described below.

Primary Hyperparathyroidism. The facts that in chronic renal insufficiency hypertrophy of the parathyroid glands occurs and that primary adenoma or hyperplasia of the parathyroid glands leads ultimately to renal disease have been the source of confusion as to which condition was primary. This subject has been clarified in the past decade, and the criteria for the diagnosis of primary hyperparathyroidism in the adult are well established.[8] We are concerned here with its occurrence during the growth period.

Primary hyperparathyroidism in children is encountered only rarely, less than a score having been reported in the literature.[18] All but three of these cases were over 10 years of age. The differentiation of this form of osteonephropathy will rarely present difficulties. The bone changes are characteristic; in the majority of the cases single or multiple bone cysts are present. Other instances show generalized osteoporosis without cyst formation, but even here the epiphyseal changes do not resemble those seen in rickets and, in fact, areas of calcification rather than decalcification are seen in the regions of active bone growth, i.e., at the epiphyseal end of the long bones.[19] Renal lithiasis and metastatic calcification are not uncommon.

A high blood calcium and low inorganic blood phosphate, as indicated in table 2, are pathognomonic. Urinary calcium is abnormally high. Renal damage is common, and after its onset the blood calcium may be somewhat reduced from the original high levels and the inorganic phosphate may increase. Although the inorganic phosphate may be normal or only slightly elevated in the presence of long standing renal damage, the calcium level will seldom be depressed to normal values. In these doubtful cases, the blood protein level and the carbon dioxide combining power should be determined, since a normal blood calcium level may be found in the presence of a low blood protein level and acidosis in hyperparathyroidism.[8]

Operative removal of the neoplastic parathyroid glands is followed by cure in cases in which renal and other damage is not too far advanced. Improvement following irradiation of the glands has been reported and may be tried when operation is impossible or refused.[18]

Cystine Storage Disease. Little is known of this condition, but the reports of several cases in which there was renal damage in conjunction with dwarfism [1] and bone changes justify its inclusion here. Cystine feeding is known to produce renal damage in the experimental animal, although the condition may not be analogous to those observed clinically in cystinuria. The pathological studies show a widespread deposition of cystine crystals in the various tissues, especially the spleen, liver and kidneys.[20]

The diagnosis of this disorder rests on the demonstration of cystine in the urine or the demonstration of crystalline deposits of cystine in the conjunctiva and cornea by examination with the slit-lamp.[4]

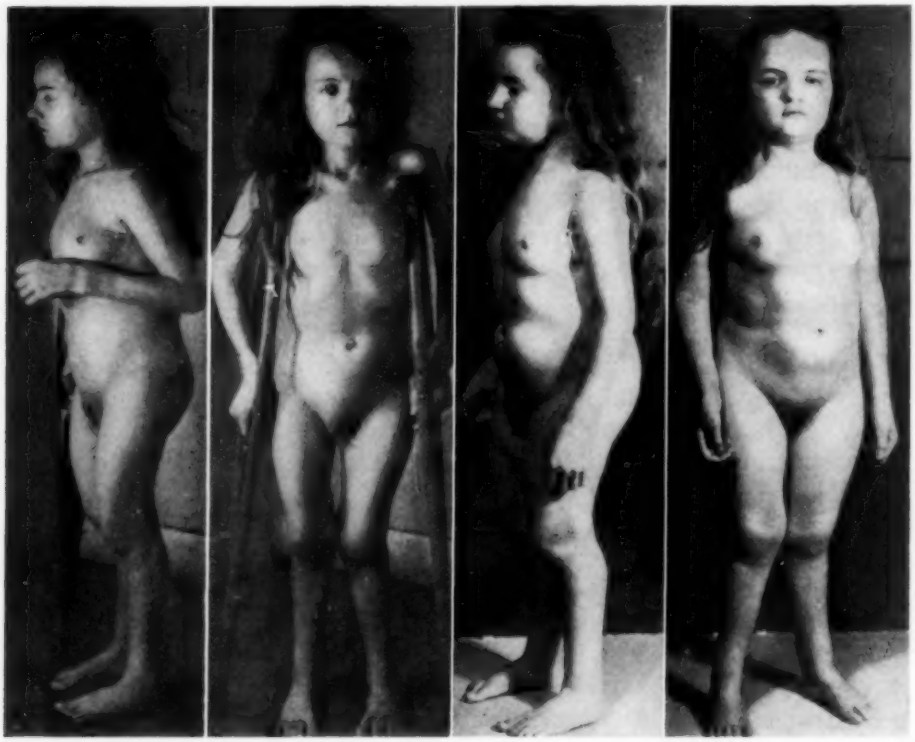
No facts regarding treatment are established.

Two cases are reported for consideration in the light of the diagnostic criteria that have been offered.

Case Reports

Case 1. J. N., a 15 year old white female dwarf, was transferred to the medical service for study after she had come to the hospital for possible orthopedic treatment.

History: Delivery was uneventful and she appeared normal at birth. Dentition was delayed and the patient did not walk until the age of three. Fractures of the left femur occurred at the age of 15 months, two years and five years and of the left radius at seven years, following insignificant trauma. At the age of 10 genu valgum had become so marked that she was unable to walk and she was admitted to a hos-



A B C D

Fig. 1. A and B are photographs taken of patient presented as case 1, during first admission to the hospital. C and D are photographs taken four months following the institution of therapy.

pital for possible correction of this deformity. A diagnosis of "renal rickets" was made and the operation was not done. However, two years before the present study the tibiae were broken manually and reset at another hospital. Although union occurred she was unable to walk following this operation. The past history was negative except for episodes of polydipsia and polyuria. Dietary history revealed no deficiencies. The menarche occurred at the age of 13 and a half; the menstrual periods had been normal. There was no history of consanguinity of the parents and none of the three living siblings show growth disturbance. Two brothers died in infancy of undetermined illness.

Physical examination: Temperature 37–37.5° C., pulse 100, respirations 20, blood pressure 100 mm. Hg systolic and 60 mm. diastolic. A photograph of the

patient is shown in figure 1. Her height was 109.2 centimeters; weight, 25.7 kilograms. She was able to take a few hesitant steps with the aid of crutches but was unable to arise from a sitting posture. Lumbar scoliosis and lordosis were marked, and there was prominence of the sternum with increase in the anterior-posterior diameter and some beading at the costochondral junctions. The long bones showed multiple curving deformities with enlargement at both ends, and hyperextensibility at the joints. No craniotabes or other deformities of the skull were evident.

The skin was sallow with patches of yellow discoloration, particularly over the forearms. There was an acneform eruption on the face. The hair was reddish with normal distribution. There was no general or local lymphadenopathy.

The pupils were round and equal, reacted actively to light and accommodation, and the extra-ocular movements were normal. Ophthalmoscopic examination revealed no opacities of the cornea, lens or media. The disc margins were sharp, the vessels normal, with no retinal or scleral deposits.

A B

FIG. 2. In A is shown a roentgenogram of the wrists previous to therapy and the result of four months therapy is shown in B. Narrowing of the epiphyseal line, growth of the centers of ossification and general recalcification will be noted.

Examination of the ears, nose, tonsils, pharynx and mucous membranes revealed nothing abnormal. The gums were retracted and livid red in color, and exudate was expressed from the gum margins. The teeth were normal in size but yellow-ivory in color, with an abnormal sheen.

Examination of the heart and lungs revealed nothing remarkable.

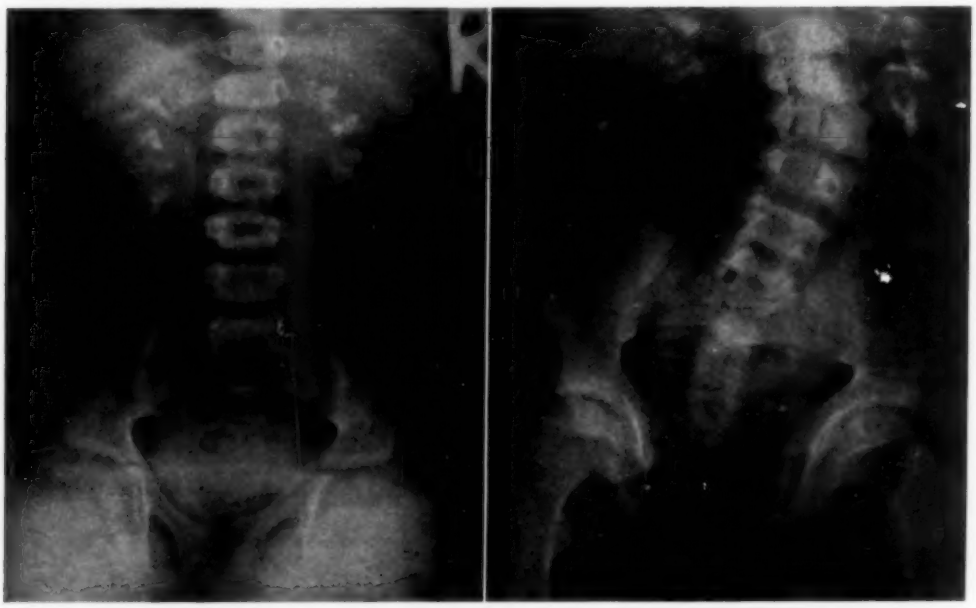
The abdomen was protuberant but otherwise normal. The external genitalia and pubic hair showed a normal adult configuration. The neurological examination was negative.

Accessory clinical studies: Roentgenographic examination of the long bones revealed extensive changes at the proximal and distal ends characteristic of rickets. The diaphyses and metaphyses showed extensive osteoporosis, and there was marked underdevelopment of all the epiphyseal centers with gross deformities of the wrists, ankles, elbows and knees resembling rickets (figure 2). A flat plate of the abdomen showed shadows of calcareous density arranged in clusters around the kidney pelves and minor calyces (figure 3).

The urine was light yellow to amber, alkaline in reaction, and contained albumin (trace to 1+) but no reducing substances. Microscopic examination of the urinary

sediment revealed 1 to 4 white blood cells, 2 to 4 red blood cells, several hyaline and granular casts per high-power field. The Fishberg test showed a maximum concentration of 1.012; the phenolsulphonphthalein excretion was 45 per cent in two hours. The urea clearance was 45 per cent of normal. A Sulkowitch test for urinary calcium showed less than normal excretion.

Blood studies showed: red blood cells, 4.6 million; hemoglobin 98 per cent; white blood cells, 7000; differential, normal. The non-protein nitrogen of the blood was 45 mg. per cent; serum calcium, 9 mg. per cent; inorganic phosphorus, 2.7 mg. per cent; blood plasma chlorides (expressed as NaCl), 735 mg. per cent and carbon dioxide combining power, 26 volumes per cent. The glucose tolerance curve was normal.



A B

FIG. 3. In A is shown a roentgenographic plate of the spine taken of the patient presented in case 1, at the age of nine years. In B is shown the progressive deformity that took place during the following six years, in spite of attempts to prevent it with orthopedic measures. The calcification of the renal pyramids is evident in both plates. (These roentgenograms and those of figure 2 are reproduced through the courtesy of Dr. J. P. Rousseau, Roentgenologist-in-Chief, The North Carolina Baptist Hospital.)

The patient was discharged on the high calcium, high phosphate, low sodium chloride diet with added vitamin D and citric acid-sodium citrate mixture, as noted above, and followed in the Out-Patient Department until readmitted four months later for further study.

The improvement noted at the time of readmission was dramatic. The patient had discarded her crutches and was able to get about and play with the children of the neighborhood. She had grown 2 centimeters in height and had gained 5 kilograms in weight (figure 1). The sallow, yellowish tint of the skin had disappeared. She was smiling, happy and playful, whereas previously she had seemed backward and lethargic.

The roentgenographic examination of the wrists and ankle joints showed marked changes in the appearance of the epiphyses, with considerable recalcification and defi-

nite evidence of healing of previous rachitic changes (figure 2). No reduction of renal calcification was evident (figure 3). The examination of the urine showed no change insofar as its content of albumin, red and white blood cells and casts was concerned. The Fishberg test revealed a concentration to 1.018, but there was no change in the phenolsulphonphthalein output. The Sulkowitch test showed a normal calcium excretion.

The blood chemical findings were: non-protein nitrogen, 30 mg. per cent; serum calcium, 11.5 mg. per cent; inorganic phosphorus, 6.0 mg. per cent; blood chloride (expressed as NaCl), 410 mg. per cent; carbon dioxide combining power, 36 volumes per cent.

Diagnosis: Osteo-nephropathy secondary to renal tubular dysfunction.

The growth of this patient following therapy is less striking than in the other reported case.[2] This is possibly related to the closure of the epiphyses at puberty, which preceded the therapy in this patient.

Case 2. N. B., a 16 month old white female infant, whose delivery was uneventful, appeared normal at birth. At the age of four months she became constipated and remained so thereafter in spite of all measures used to stimulate normal bowel evacuation. The abdomen began to increase in size at this time. At seven months she had a respiratory infection associated with otitis media and a mild degree of anemia. At this time albumin was first found in the urine. Glycosuria first appeared at the age of one year, although a fasting blood sugar taken at that time showed a level of 77 mg. per cent. She had not made any effort to bear weight on her legs, and despite large doses of vitamin D, developed signs of rickets. Physical examination revealed a normally proportioned infant 77.5 centimeters in length. Marked craniotabes was present, as well as a beading at the costochondral junctions and flaring of the costal margins. Examination of the heart and lungs was negative. There was a moderate protrusion of the abdomen, and the liver was palpable at two fingers' breadth below the costal margins.

The urine was light yellow in color, reaction alkaline; specific gravity 1.010; albumin, trace to 2+; sugar, 2+ to 4+. Microscopic examination revealed 20 to 30 red blood cells, 10 to 20 white blood cells and several granular casts per high power field. The Sulkowitch test for urinary calcium revealed less than normal excretion.

The blood study revealed: red blood cells, 4.7 million; white blood cells, 9400 with 52 per cent lymphocytes; hemoglobin 95 per cent. The blood chemical findings were: serum calcium, 12 mg. per cent; phosphorus, 3.2 mg. per cent; carbon dioxide combining power, 39 volumes per cent; plasma chlorides (expressed as NaCl) 595 mg. per cent.

Roentgenographic examination of the long bones revealed indistinct outlines of the epiphyses which were undeveloped and decalcified with marked widening of the epiphyseal line, characteristic of active rickets. A flat plate of the abdomen revealed moderate enlargement of the hepatic and splenic shadows. Intravenous and retrograde urography showed bilateral rotation and hydronephrosis, the dilatation being most marked on the right side. The left ureter was dilated and tortuous. The bladder was small and showed a persistent inverted funnel-shaped deformity. On urologic examination a No. 14 Butterfield cystoscope passed easily into the bladder. The bladder was normal throughout except for a pale mucosa. Each ureteral orifice was normal as was the vesical neck. A No. 4 catheter passed to each renal pelvis without meeting obstruction.

A diagnosis of osteo-nephropathy due to renal disease was made. In view of the acidosis associated with normal chlorides, the glycosuria and the values for calcium and inorganic phosphate, this case appears to be of the type described by deToni [10] and Fanconi.[11] The patient was placed on a high potassium diet with added dicalcium phosphate and vitamin D and potassium citrate buffer solution.

Summary

1. The association of bone and renal disease which has been called "renal rickets" is composed of a number of clinical entities. The term "osteonephropathy" is suggested for this syndrome, and criteria for the differentiation of the various forms of this disorder are summarized.

2. Two cases are presented, one with marked improvement following therapy.

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CARCINOMA AND LEUKEMIA: REPORT OF TWO CASES WITH COMBINED LESIONS: REVIEW OF LITERATURE*

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RECENT observations of two cases of carcinoma associated with leukemia encountered within a period of seven years prompted us to make a brief survey of this rare phenomenon. Since 1913 there have been about 600 cases of leukemia in this institution.

The occurrence of leukemoid reactions in malignancy has been stressed previously [15, 17, 19] and need not concern us here. Lymphosarcoma and an associated lymphatic leukemia have been regarded as a single entity by Stern-

TABLE I

Author	Year	Number of Cases	Type of Leukemia	Type of Malignancy
1. Bruckner	1934	1	lymphatic	Portio carcinoma
2. Burg	1924	1	myelogenous	ca. of stomach
3. Cabot case	1933	1	myelogenous	metastatic ca. of lungs
4. Denoyer	1936	1	lymphatic	ca. of larynx
5. Ferrero and Gedda	1933	1	myelogenous	fibrosarcoma
		1	lymphatic	angiosarcoma
6. Fuhs	1927	1	lymphatic	basal cell epithelioma
7. Genevrier, Lorrain and Coirre	1930	1	lymphatic	epithelioma of lung
8. Gittins and Hawksley	1933	1	monocytic	ovarian endothelioma
9. Hanns and Sacrez	1934	1	myelogenous	lymphosarcoma
10. Heim	1933	1	myelogenous	portio carcinoma
11. Lannois and Regaud	1895	1	lymphatic	ca. of uterus
12. Marischler	1896	1	lymphatic	hypernephroma
13. Scheuffer	1933	1	lymphatic	epithelioma of skin
14. Schreiner and Wehr	1934	4	lymphatic	basal cell ca. of nose epithelioma of ear ca. of lung ca. of breast
15. Shal	1933	1	lymphatic	ca. of peritoneum
16. Whipham	1878	1	lymphatic	ca. of liver and pancreas
17. Zadek	1933	1	myelogenous	myeloma ? ca ?

berg [27] and others.[1, 29] A case of reticulum cell sarcoma associated with lymphatic leukemia reported by Richter [23] also falls into this category. Furthermore, cases of chloroma with leukemia [11, 21, 31] are not considered in this survey. The first authentic instance of the simultaneous occurrence of malignant disease and leukemia was reported by Whipham in 1878.[28] Schreiner and Wehr [25] reported four cases of leukemia among the records of 11,212 cases of malignancy, and Hoffman [14] three cases of malignancy

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among 174 cases of leukemia. In all, 21 cases of combined leukemia and malignancy have been reported to date (table 1). This contribution brings the total to 23. One case was of the myeloid, and the other of the lymphatic type. Of the previously reported cases, 14 were of the lymphatic, six of the myeloid and one of the monocytic variety.

Case Reports

Case 1. Patient A. N., male, 62 years of age, was admitted to the Jewish Hospital on December 12, 1940, presenting a history of loss of weight, increasing constipation, rectal bleeding and pain of four months' duration. His past history was irrelevant except for a transurethral prostatectomy which had been performed four years previously at the Mount Sinai Hospital, New York. There was no evidence of leukemia at that time.

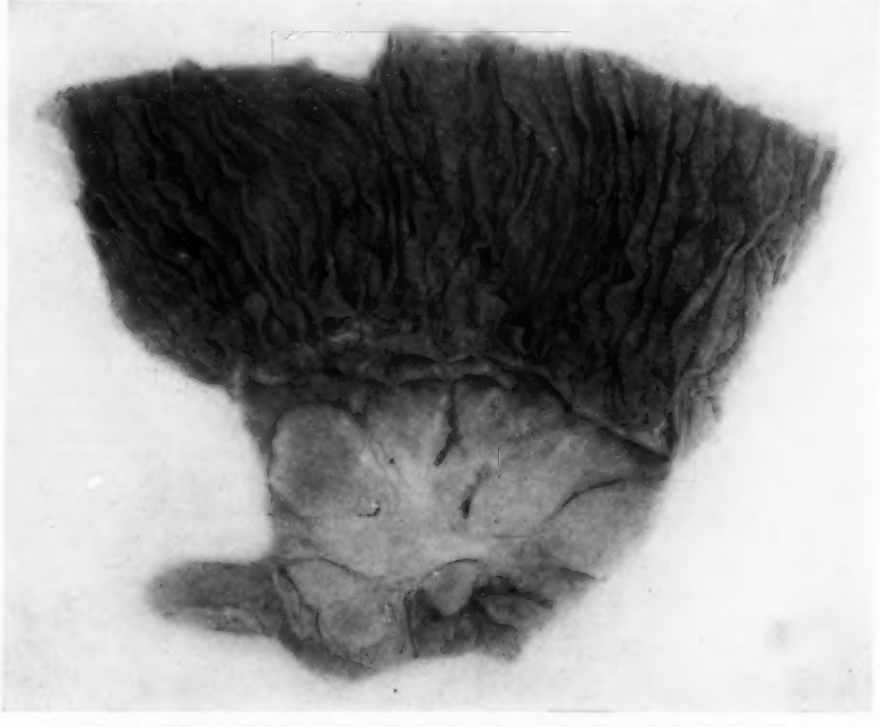

Fig. 1. Enlargement of mesenteric lymph nodes; lymphatic leukemia.

Physical examination on admission revealed an elderly white man who appeared chronically ill. There was evident weight loss. The heart and lungs showed no abnormalities. The abdomen was moderately distended in its lower half. The prostate was small. A crater ulcer was felt on the postero-lateral wall of the rectum. This measured 4 by 4 cm. and was situated one and one half inches above the anus. The edges were firm and somewhat polypoid. Proctoscopic examination confirmed these findings. A biopsy was taken and the pathologic report was adenocarcinoma.

At operation, December 14, 1940, the liver was found to be normal in size; its surface was smooth. A few adhesions were present in the region of the gall-bladder.

The gastrointestinal tract down to the rectosigmoid was normal. A few soft nodes were palpable along the anterior abdominal aorta but none was felt along the lower aorta or the iliacs. On palpation of the posterior rectal wall a small firm mass was felt just below the peritoneal reflection. This was interpreted as the upper limits of the rectal lesion. The sigmoid was moderately redundant. An abdomino-perineal resection was done.

Summary of microscopic findings by Dr. D. Grayzel (figure 5): The tumor was composed of numerous, various-sized lumina lined by cylindrical cells of varying size

FIG. 2. Carcinoma of head of pancreas with dilatation of biliary passages.

and shape, containing vesicular or hyperchromatic nuclei some of which were in mitotic division. There was piling up of these cells in places, with loss of cell polarity. The tumor was seen extending between bundles of smooth muscle cells. A preparation from the regional lymph nodes showed the cytoarchitecture completely replaced by tumor tissue which was similar in structure to that described above.

Hematological studies (table 2) revealed a slight anemia, hyperchromic in type, with a tendency to leukopenia. There was a relative polynucleosis. No abnormal cells were seen. The hematocrit was 35 per cent.

Under supportive therapy the wound granulated in from the bottom. The patient gained in weight from 110 to 125 pounds during a period of 15 months, while under

observation in the outpatient department. On his visit of April 27, 1942, he complained of a cough of two weeks' duration, pain on the right side of the head, and a loss of weight of 11 pounds in the preceding two months. The colostomy was func-

TABLE II

	Date	Hemoglobin	Red Blood Cells	White Blood Cells	Myeloblasts	Polymorphonuclear Neutrophiles	Lymphocytes	Monocytes
Case 1	12–14–40	74	3.35 million	5,280		74	26	
Case 1	5–14–41	35	1.45 million	1,650	97		3	
Case 1	5–19–41	48	2.27 million	6,500	100			
Case 2	4–19–35	78	3.8 million	66,000		13	78	9
Case 2	6–17–35	47	2.4 million	48,000		35	65	

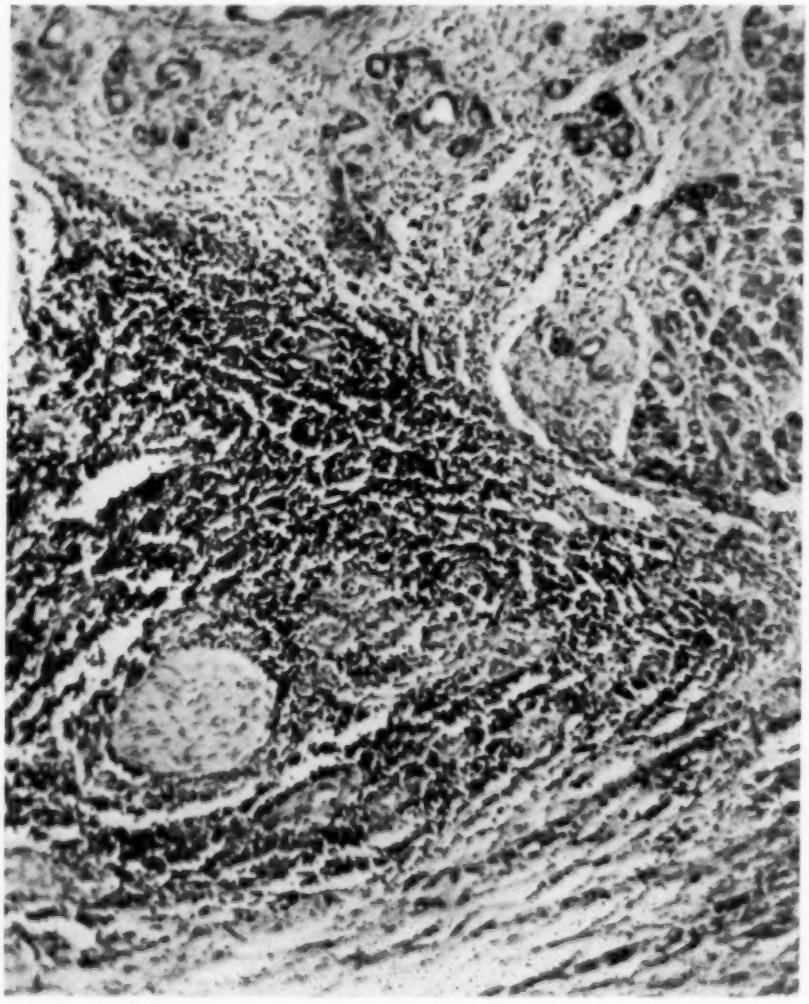

FIG. 3. Lymphatic infiltration of pancreas.

tioning well. No abdominal masses were felt; the liver dullness extended two fingers'-breadth below the costal border but was not palpable. Roentgenographic studies of the skull and ribs showed no evidence of metastasis. There was a broadening of the right, superior mediastinal shadow.

On May 11, 1942, the patient returned to the clinic complaining of a discharging ear and pain, chills and fever. He was readmitted to the hospital and presented, on admission, a purulent exudate in the right auditory canal. The drum was gray-

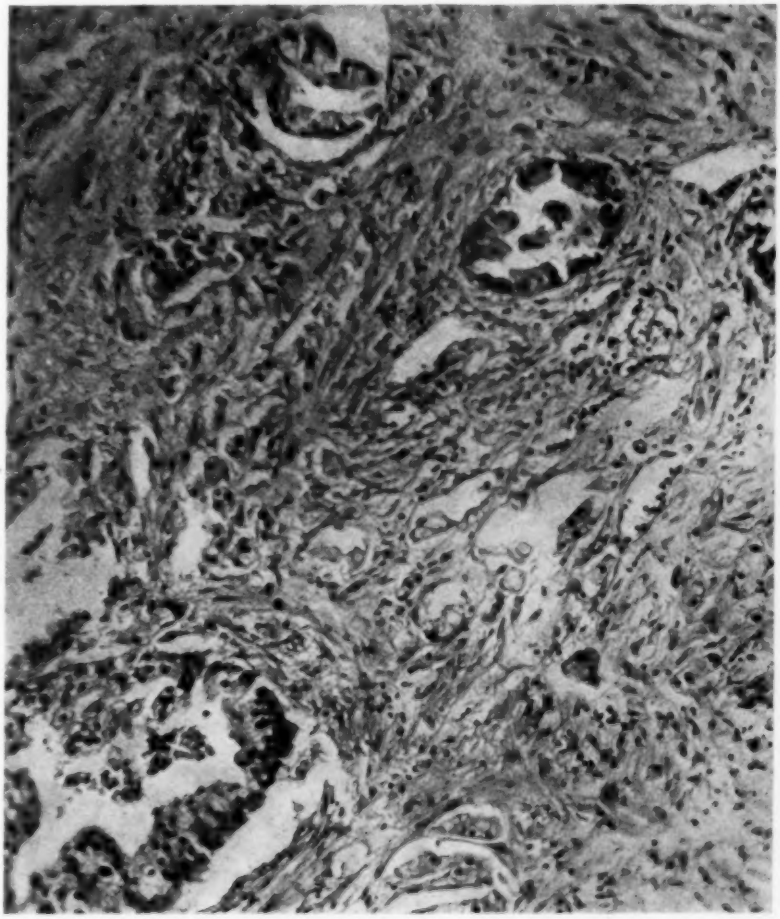

FIG. 4. Carcinoma of head of pancreas.

red and slightly thickened. There was a perforation in the posterior half, emitting a pulsating discharge. The mastoid was not tender and there was no evidence of periostitis. The left ear was normal. The nose, throat, and sinuses were normal.

There were dullness and diminished breath sounds over the base of the left lung. The liver and spleen were not palpable. There was no significant adenopathy and no petechiae. There was some heaping up of the gums. Hematologically (table 2), there was a myeloblastosis of the bone marrow and in the peripheral blood (figure 6). There was a peripheral leukopenia. The patient did not improve with symptomatic and supportive therapy and died one week later. No autopsy was obtained.

Summary. An elderly white patient had an adenocarcinoma of the rectum, corroborated by biopsy and at operation, and later by microscopic examination of the specimen. The blood did not then reveal any evidence of leukemia. Bone marrow studies were not done on the first admission. The patient made an uneventful recovery for 15 months, only to return with evidences of myeloblastic leukemia of the leukopenic variety. This was corroborated by bone marrow studies. From the present study one would assume that the carcinoma preceded the leukemia. However, since no bone marrow studies were included in the first admission, it is not possible to

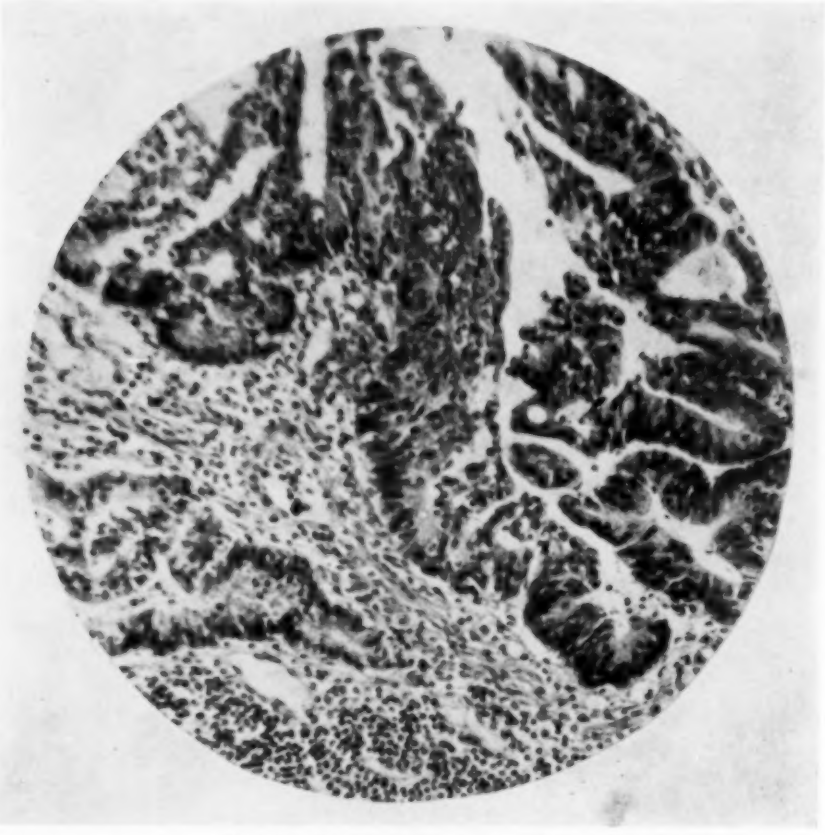

FIG. 5. Adenocarcinoma of rectum.

be positive on this point. Because of the marked myeloblastosis in the bone marrow and peripheral blood stream a malignancy with a leukemoid reaction may be excluded.

Case 2. Patient A. S., male, 58 years of age, was admitted to the Jewish Hospital on April 18, 1935, because of vague abdominal pain. This began about three weeks prior to admission. At first the pain was situated in the left upper quadrant. It lasted for two hours and was relieved by an enema. Two weeks later he developed a constant pain in the right upper quadrant. This sometimes radiated to the right scapular region. In addition there was a burning sensation in the throat and a loss of appetite.

On examination the patient showed some emaciation and icteric sclerae. There was generalized lymphadenopathy involving cervical, axillary, inguinal, femoral and epitrochlear nodes. These were firm, discrete, non-tender and, for the most part,

large. The liver was felt four fingers' breadth and the spleen one and one half fingers' breadth below the costal border, firm and non-tender. The heart and lungs were normal. Roentgenogram of the chest revealed a dense, bilateral hilum infiltration and a mottling in the left apical region suggestive of healed tuberculosis. The urine contained bile. Moderate amounts of urobilinogen were found in the urine and in the stools. The icterus index was 25.

During his hospital stay there were no substantial changes in his status, except that his gall-bladder became palpable and the jaundice increased. He was given

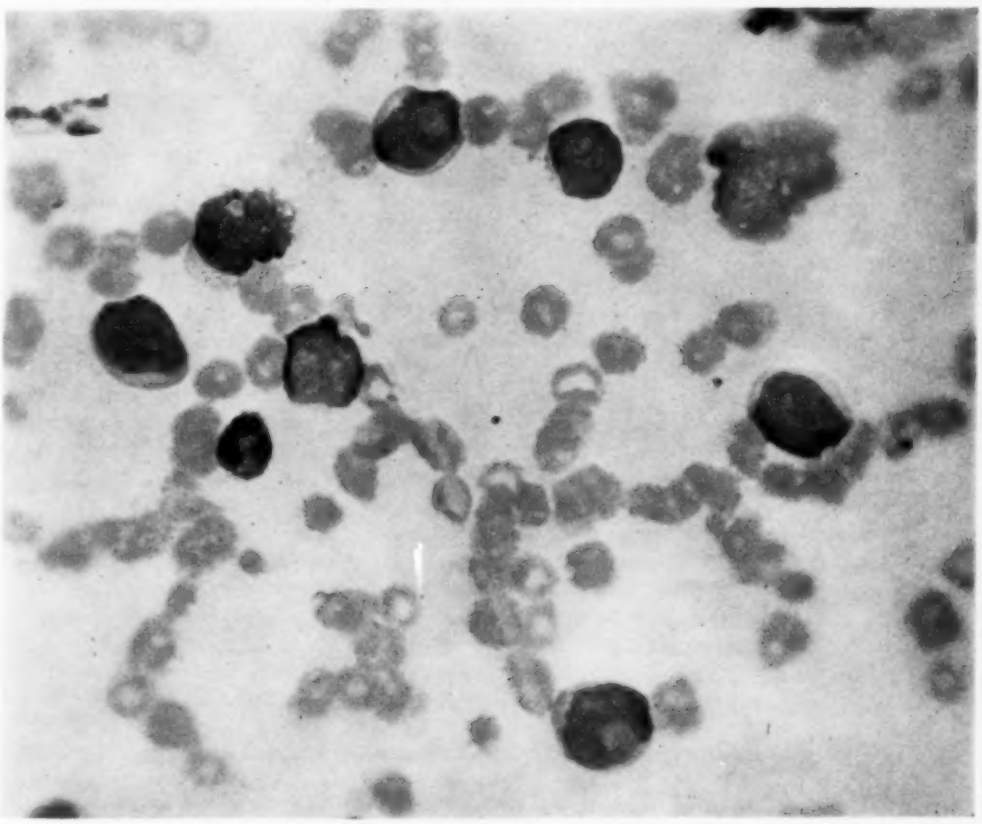

FIG. 6. Myeloblastic leukemia.

roentgen therapy to the pituitary gland. This was done on the assumption that shrinking of the latter might diminish the secretion of the growth hormone and thus affect, in a general way, the tendency to lymphatic hyperplasia. He was discharged unimproved after a stay of 18 days.

He was observed in the roentgenological clinic where he was given three roentgen-ray treatments to the pituitary. He subsequently developed uncontrollable diarrhea which persisted for three weeks. Weakness and anorexia became extreme. He was readmitted on June 17, 1935. During his second stay, his temperature, which had been normal before, began to rise to 102–103° F. daily. He received a transfusion of whole blood the day after his admission and another 12 days later. His strength gradually failed and he died 31 days after his second admission, three months after the onset of his symptoms.

On his first admission the hematological findings (table 2) were a leukocytosis of 66,000 with a relative lymphocytosis of 78 per cent. On the second admission there was a marked fall in hemoglobin, from 78 per cent to 47 per cent. There was a reduction in the leukocytosis but a lymphocytosis with a preponderance of immature cells prevailed. The icterus index rose to 35. The bilirubin was direct immediate positive.

Summary of autopsy findings: Lymph node enlargement, generalized (figure 1), lymphocytic infiltration of lungs, liver, gall-bladder, spleen, suprarenals, kidneys and bone marrow, lymphocytic infiltration of pancreas: carcinoma of head of pancreas (figure 2), obstruction of pancreatic and biliary ducts, dilatation of the pancreatic duct, the intrahepatic biliary ducts and gall-bladder with icterus; emaciation, decubital ulcer over sacrum, apical scars of lungs.

Microscopic findings in the pancreas (Dr. M. Lederer): In a preparation from the head of the pancreas (figure 3) the architecture was completely replaced by extensive accumulation of small round cells with darkly-stained nuclei and intervening broad sheets of young, fibrous connective tissue, through which were scattered similar small cells. In places, imbedded in a dense, hyalinizing, fibrous connective tissue there were numerous small and large spaces, representing pancreatic ducts, lined by a much folded epithelium of tall columnar cells with basally placed nuclei. Occasional barely recognizable remnants of acinar and islet cells were surrounded by fibrous tissue, or by a mass of small round cells.

In other preparations of the head of the pancreas (figure 4), there were imbedded in a loose, fibrous connective tissue stroma, ill-defined, tubular and acinar structures composed of cylindrical cells, varying in size and shape and depth of stain, with single large vesicular or hyperchromatic nuclei, among which were numerous mitotic figures. In places the cells were heaped up into multiple layers. Preparations from peripancreatic nodes revealed no trace of metastatic lesions resembling those in the head of the pancreas.

Summary. A white male patient was admitted for leukemia and jaundice which at first was believed to be caused by enlarged lymph nodes obstructing the bile ducts, but which eventually was explained on the basis of a carcinoma of the head of the pancreas. It is undeniable that in this case a malignancy supervened in a patient with an old chronic lymphatic leukemia.

Comment

It is not at all improbable that some cases showing these associated lesions have escaped notice. It is felt that henceforth their incidence will be recognized more frequently because of more thorough examinations including bone marrow studies. This is particularly true because of the common and almost routine resort to bone marrow aspirations, as well as splenic aspirations. The demonstration of malignant cells in the bone marrow in otherwise unsuspected cases is becoming increasingly frequent. This will also lead to finding evidence of leukemia more frequently in bona fide cases of malignancy.

There does not seem at present to be any organ or tissue outstandingly involved in these cases. Malignancy involving the skin, muscles, stomach, trachea, lungs, pleura, breast, ear, nose, uterus, ovaries, kidneys, peritoneum and blood vessels have been reported (table 1) in association with leukemia. Both of our cases were connected with the gastrointestinal tract. Interesting are the instances of epithelioma of the skin which developed from a

leukemid.[8, 24] The association of different types of malignant disease, as well as the combination of leukemia and malignancy is rare. In case 1 of our report the time relationship of the two diseases is not clear; in case 2 the leukemia antedated the cancer. It is hard to expect a causal or etiologic relationship. The question of whether leukemia is a form of malignant disease is still debatable. It has even been felt that leukemia may be a deficiency disease.[20] It appears that lymphatic leukemia is more commonly associated with malignancy than other forms of leukemia, but not enough cases have been studied for these observations to be significant. Jaundice in leukemia is ascribable to a cause other than the leukemia.

Summary

1. A review of the reported cases of cancer associated with leukemia is presented.

2. A case of adenocarcinoma of the rectum complicated by myeloblastic leukemia and a case of chronic lymphatic leukemia complicated by a carcinoma of the head of the pancreas are presented.

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THE RENAL LESION IN RHEUMATIC FEVER*

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Since Rayer [1] emphasized the nephritic complications of rheumatic fever there have been numerous observations, all of which note the infrequency of clinical evidence of renal involvement during the active stages of this disease. In a large series of cases the incidence of nephritic complications varies between 0.67 and 7 per cent.[2, 3, 4, 5, 6, 7, 8, 9, 10] Despite this, Bell [11] finds cardiac rheumatism and nephritis to be frequent in necropsy material. In necropsies of 104 cases of rheumatic valvulitis showing active lesions, he found renal involvement in 24.9 per cent, 22 per cent of which showed acute diffuse glomerulitis. He does not state whether clinical evidence of nephritis was present in these cases or whether Aschoff bodies were found at post mortem.

Although during the past 14 years 1622 patients entered the hospital with the admission diagnosis of acute rheumatic heart disease, the clinical diagnosis of rheumatic nephritis was not made during this period.

Three thousand necropsies were performed, among which 153 presented rheumatic cardiac disease as the principal cause of death. Four cases were observed with active rheumatic endocarditis and myocarditis with Aschoff bodies, and renal lesions which we believe were caused by the etiological agent of rheumatic fever. In two cases renal involvement was probably the most significant cause of death. Our first case presented a unique vascular lesion involving the coronaries as well as the renal arteries.

Case Reports

Case 1. Acute and chronic rheumatic endocarditis with clinical picture of abdominal rheumatism. Development of hypertension while under observation with severe convulsive seizures. Necropsy: Rheumatic heart disease with Aschoff bodies. Hyperplastic endarteritis of coronary and renal vessels. Bilateral renal infarctions.

Clinical history: C. P., Italian housewife, aged 31, was admitted to Lincoln Hospital, June 14, 1933, because of convulsive seizures. Present illness began two months before admission when she developed joint pains involving both knees and ankles. The right knee joint became extremely swollen and inflamed. A hemorrhagic eruption was noted over chest and arms. Six weeks before admission severe right upper quadrant pain developed, a diagnosis of empyema of the gall-bladder was made, and cholecystectomy had been performed at a private sanatorium. No significant gall-bladder disease was found, according to the operative record. Histological examination of this organ was not made.

One month prior to admission she was again hospitalized, because of persistent abdominal and joint pains and "bloody urine." The patient was noted to be acutely

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ill with marked epigastric pains and marked tenderness in the right lumbar region. A roentgenogram of the genito-urinary tract revealed no significant findings. Blood examination: Red cells 4,300,000, hemoglobin 85 per cent, white cells 8,900 with 80 per cent polymorphonuclear neutrophiles, and 20 per cent lymphocytes. Urinalysis: specific gravity 1.015, reaction acid, trace of albumin, no sugar. Six pus cells were seen per high power field. Discharge diagnosis was "pyelonephritis."

She was then treated at home by her private physician. Her temperature continued high, and a generalized purpuric rash appeared, followed by convulsive seizures. At this time the blood pressure was found to be greatly elevated, although her physician had always obtained normal readings previously.

Clinical examination at Lincoln Hospital revealed the patient to be critically ill, comatose, with generalized convulsive seizures lasting from three to five minutes. Temperature was 98.3° F., and the pulse 110 per minute with gallop rhythm. Respirations were 28–30 per minute. There was papilledema of the left disc with two hemorrhages. The right disc was congested; otherwise it was normal. No murmurs were audible. Blood pressure was 230 mm. Hg systolic and 100 mm. diastolic. The biceps, triceps and abdominal reflexes were absent. Knee jerks were present and equal. Babinski reflex was indecisive.

Laboratory data: Urinalysis showed marked albuminuria, casts and numerous red cells and pus cells. Hemoglobin was 80 per cent. Red cells were 4,800,000 per cu. mm. White cells totaled 23,000 with 90 per cent polymorphonuclear neutrophiles. Blood chemical tests were within normal limits. By lumbar puncture 20 c.c. of clear fluid were removed under increased pressure. Count showed 16 cells per cm. Smear and culture were negative.

Phlebotomy was attempted, but only 4 oz. were removed because of technical difficulties. Intravenous injection of 50 per cent glucose solution and an ampule of calcium gluconate were given. The convulsions persisted. By another lumbar puncture 30 c.c. of clear fluid under increased pressure were removed followed by numerous convulsive seizures. In the afternoon of the same day, left hemiplegia and weakness of right leg developed. Convulsions continued at intervals during the night. The following morning temperature rose to 104° F., and signs of pulmonary edema developed, followed by death, 30 hours after admission.

Clinical diagnoses: Acute glomerulonephritis and hypertensive encephalopathy.

Postmortem examination (summary): The body was that of a well developed, well nourished, young woman. There was a fading hemorrhagic eruption over the anterior part of the chest. A considerable portion of the left pleural cavity was obliterated by thin adhesions which were easily separated. There were numerous subpleural hemorrhages. The lungs were crepitant throughout, except for several scattered, small, firm, reddish-gray areas.

The heart weighed 250 gm. The left ventricular musculature was increased in breadth, measuring between 2 and 2½ cm. The anterior and posterior muscles of the mitral valve were broad and thick. The left auricle was dilated with thickened white opaque endocardium. The mitral valve showed moderate fibrosis of the cusps and chordae tendineae, but there was no stenosis. The aortic cusps were normal.

Along the line of closure of the auricular aspect of the anterior cusp of the mitral valve were typical rheumatic verrucae, forming a row of small vegetations uniform in size and more or less confluent. The right and left coronary arteries were firm and rigid. Transverse section at various levels of these vessels showed almost complete obliteration of their lumina by firm tissue without atheroma, ulceration or calcification. Sections throughout the myocardium showed all the branches of these vessels to be similarly involved.

Both kidneys were of normal size and presented identical lesions. The capsule was thickened, and stripped with difficulty leaving a very irregular and nodular surface. There was almost complete infarction of the cortices of both kidneys. The

surface color was a mixture of chocolate brown and grayish white. Brown areas were irregularly shaped and depressed. Grayish areas were elevated and confluent and showed a finely granular surface. The cut surface of both kidneys presented similar color contrasts. The cortico-medullary relationship was disturbed and the markings were obscured. The interlobular vessels were extremely prominent and showed dense thick walls with small central lumina, resembling the coronary arteries.

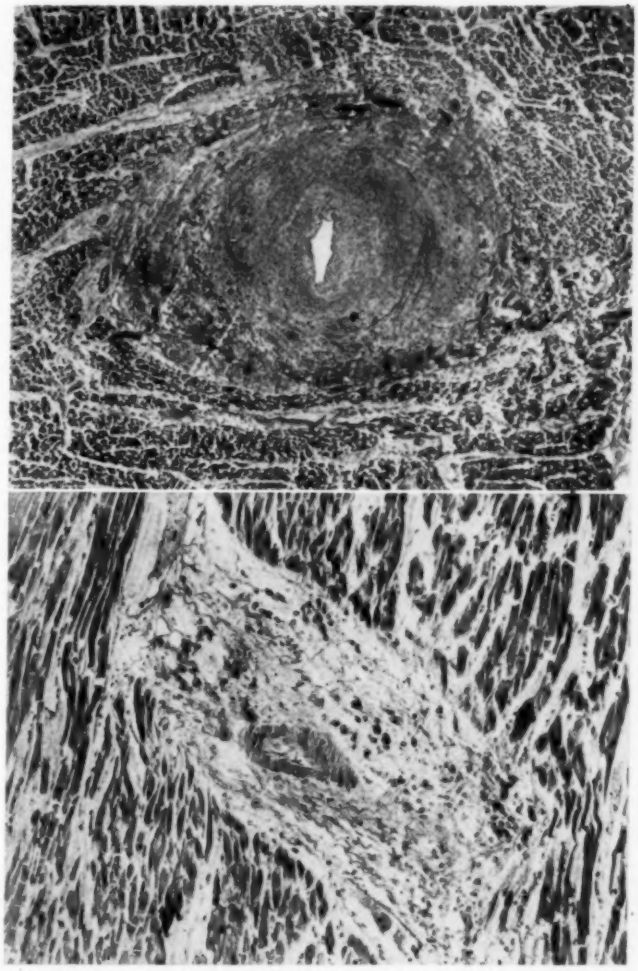

FIG. 1. (*Above*) Case 1. Branch of descendens of left coronary artery. Obliteration of lumen and replacement of media by fibrous tissue. A few muscle bundles persist of the periphery.

FIG. 2. (*Below*) Case 1. Typical myocardial Aschoff body.

The spleen was not infarcted. The cerebrum was markedly edematous with flattened convolutions. There were a few superficial ecchymoses only. The basilar vessels were normal.

Anatomical diagnoses: Acute and chronic rheumatic valvulitis; hyperplastic endarteritis of the coronary arteries; hyperplastic endarteritis of the interlobular renal arteries; bilateral renal infarctions; acute cerebral edema; bronchopneumonia.

Microscopy: The heart muscle showed considerable fibrosis both interfascicular and perivascular. Typical Aschoff nodules and cells were frequent in sections of the myocardium and predominantly perivascular. These cells varied in size and shape. All showed basophilic cytoplasm and deeply staining, large, irregularly shaped, single or multiple nuclei (figure 2).

Sections including the mitral valve ring and cusps showed diffuse thickening due to fibrosis and collagenous swelling and fragmentation with superficial verrucous hyaline deposits, bacteria free. There was increased vascularization of the ring with inflammatory cell infiltrations and Aschoff bodies.

The right and left coronary arteries and their branches showed unusual features. The lumina of these vessels were almost obliterated by an excess of compact subintimal fibrous tissue showing a fibrillar structure and a moderate number of nuclei (figure 1). The cytoplasm of these cells was basophilic and of various size and shape. Many had long stellate anastomosing processes. Some cells had large nuclei, containing one or more nucleoli and resembled Aschoff cells. The internal and external elastic lamellae were not evident. Diffuse fibrous replacement of the media was apparent throughout all sections of the coronary vessels. Surrounding the ramus descendens of the left coronary was a broad and wavy area of fibrous tissue. At some levels this layer was at least twice as thick as the diameter of the vessel itself and contained numerous thick-walled vessels and veins, many of which were surrounded by similar periarterial areas of fibrosis, infiltrated with lymphocytes, plasma cells and numerous typical Aschoff cells.

The capsule of the kidney was thickened. The cortex was quite disorganized by old and recent infarctions. The former consisted of areas of rather acellular fibrous tissue, whereas others of more recent origin were cellular and vascularized. The latter were in the process of organization. Within some of these areas fibrosed and hyalinized glomeruli and degenerated tubules persisted. The lumina of the interlobular arteries and portions of the arcuate artery were more or less completely obliterated by a dense intimal proliferation of collagenous fibrous tissue containing a moderate number of stellate shaped cells with long anastomosing processes (figure 3). Some of these cells were quite large with cytoplasm more or less basophilic. Others contained large, irregular nuclei and resembled Aschoff cells. Similar fibrosis partially replaced the muscular layers and extended into the adventitia and often far beyond the confines of this layer. Here large vessels showed endarteritic closure, similar to the main trunk, and some were enveloped by fibrous tissue containing many newly formed capillaries. Many vessels were canalized and some thrombosed. A small segment of one of the arcuate vessels showed suggestive aneurysmal formation. Here the muscular coats were partially interrupted and were partially lost within fibrous tissue similar to that filling the irregularly dilated lumen of the vessel.

The glomeruli varied considerably in size. Nearly all were smaller than normal. Many showed fibroblastic proliferations of the capsule and some were constricted into lobular divisions by fibrous tissue. The capillaries of the tufts were filled unevenly with red cells. Many glomeruli were partially or completely collapsed. Some of the vasa afferentia were dilated with more or less hyalinization of their walls.

Section of the cerebrum showed severe edematous distention of Virchow-Robin spaces and a diffuse capillary encephalorrhagia.

Histological diagnoses: Chronic and acute rheumatic endocarditis of the mitral valve; rheumatic arteritis involving the coronary and renal vessels; multiple bilateral infarctions of the kidneys; encephalorrhagia.

Comment. We believe that the bizarre symptomatology in this case was caused by diffuse obliterative vascular disease with multiple visceral infarctions, most likely of rheumatic origin. The similarity of the cardiac and

renal lesions lends support to our belief that both were caused by the same etiological agent, namely, rheumatic fever. Similar cases have been described by Klinge.[12] Severe convulsive seizures occur in the so-called cerebral forms of rheumatic fever, although the sudden onset of hypertension, which probably resulted from bilateral renal infarctions, may have been responsible for these episodes in our case. Leiter's[13] case showing obliterative renal lesions with multiple renal infarctions likewise developed hypertension quite suddenly. In his case the nature of the vascular changes was obscure.

Numerous clinical and histological studies[14, 15] have been made of the coronary arteries in rheumatic fever and changes similar to those present in our case have been described.

Slater[16] observed a patient who presented symptoms and signs of acute coronary occlusion followed by acute polyarthritis, relieved by salicylates. Complete recovery followed. Slater believed that the patient's thrombosis was caused by rheumatic arteritis of the coronary vessels. Perry's[17] patient, a 14 year old girl, suffered severe angina pectoris. The coronaries were found to be occluded by a hyperplastic intimal lesion. Aschoff bodies were numerous in the myocardium.

Friedberg and Gross[18] reported four autopsied cases in which diffuse renal vascular lesions, typical of periarteritis nodosa, were found associated with rheumatic fever and rheumatic myocarditis with Aschoff bodies. These cases presented clinical signs of carditis, joint pains, urticarial or hemorrhagic skin eruptions, uremia and abdominal pains in varied proportions. Cases 2 and 3 were subjected to exploratory laparotomies because acute appendicitis was suspected. All cases were autopsied. Necrotizing arteriolitis was observed on histological study. Renal arteritic and periarteritic infiltrations of the acute type were present resembling the lesions of malignant nephrosclerosis. These authors believe that rheumatic fever is the etiological agent in many cases of vascular disease considered to be periarteritis nodosa of idiopathic origin.

Case 2. A 12 year old girl was admitted with symptoms and signs of decompensated rheumatic heart disease and acute arthritis. Blood cultures were sterile. Blood nitrogen was elevated. Postmortem examination disclosed rheumatic verrucae, bacteria free, and Aschoff bodies, fibrinous pericarditis, renal arteriolar necroses, arteritis and focal glomerulitis.

Clinical history: L. L., aged 12, female, was admitted to the pediatric service December 27, 1940, because of arthritis, dyspnea and cyanosis. The patient had had "rheumatism" for the preceding two years, suffering from recurrent bouts of fever, arthritis, fatigue, dyspnea and cough. She had been hospitalized in another institution five years previously for similar complaints. Four days before admission swelling of legs and abdomen occurred quite suddenly.

Examination revealed the patient to be severely ill, dyspneic and orthopneic. Temperature was 102° F. Respirations were 28. Pulse was 130 per minute. Blood pressure was 136 mm. Hg systolic and 70 mm. diastolic. The conjunctivae were of a faint, subicteric color. There was a heaving cardiac impulse and the heart was enlarged to percussion. Apical systolic and diastolic murmurs were heard. The

lungs were congested. The liver was enlarged four fingers' breadth below the costal margin. The spleen could be easily palpated. There was moderate ascites. Temperature varied between 100 and 103° F.

Eleven blood cultures were sterile. Urinalyses showed many red cells and pus cells, albuminuria and occasional granular casts. Hemoglobin was 60 per cent on admission and eventually reached 54 per cent. Red cells numbered 2.5 million. Smear showed a microcytic hypochromic anemia. Leukocytes varied between 6,000 to 15,000 with 60 to 68 per cent polymorphonuclear neutrophiles. Roentgenogram showed marked enlargement of the cardiac shadow on both sides. Electrocardiographic report was "myocardial damage and A. V. conduction increase." Temperature varied between 100 and 103° F. Petechiae were noted on several occasions in the mucous membranes of the mouth. Under therapy, the patient improved considerably and was discharged on February 26, 1940.

The patient was readmitted on April 16, 1940, because of similar complaints. Temperature was 100° F. Pulse was 72, completely irregular. Respirations were 32. There were signs of pulmonary congestion with severe pain in right chest. Under observation the temperature rose to 103° F., and the patient became severely dyspneic and cyanotic. Electrocardiographic report: "PR interval of 0.2 sec. R. axis deviation." Total non-protein nitrogen was 101.28 mg. with blood urea of 58 mg. per 100 c.c. Leukocytes numbered 22,000 with 73 per cent polymorphonuclear neutrophiles. The urine showed numerous red cells and pus cells. Numerous blood cultures were sterile. Despite therapy, decompensation increased in severity and the patient died on May 6, 1940, five months after first admission.

Clinical diagnoses: Chronic rheumatic cardiac disease with acute terminal valvulitis; pulmonary infarction; subacute bacterial endocarditis (?).

Postmortem examination (summary): There were extensive pleuropericardial adhesions. Both pericardial layers were adherent over large portions of their surfaces. The uninvolved areas were covered by a fibrinous exudate. The heart and pericardium weighed 610 gm. All cavities were dilated with hypertrophied musculature. The mitral valve showed old fibrosis and deformity with thickening of chordae tendineae. There was a row of typical rheumatic verrucae on the free edge of the posterior cusp of the mitral valve. These were fairly firm and partially healed. The aortic valve showed scarring and deformity with fusion of commissures and rolling of the free edges.

The lungs showed diffuse induration and areas which were firmer, whiter and more elevated than the adjacent parenchyma. Both kidneys were swollen, each weighing 150 gm. Cortical surfaces were smooth but showed numerous small, petechial hemorrhages. The spleen weighed 350 gm. and showed two small, rectangular, circumscribed areas each 2 by 2 cm. Examination of the other viscera revealed chronic passive congestion.

Anatomical diagnoses: Rheumatic pancarditis, healed and active stages, with mitral stenosis; acute glomerulonephritis; bronchopneumonia; infarcts of spleen.

Microscopy: Section of posterior mitral cusp showed small verrucae on the line of closure, composed of pink staining fibrillar material with few nuclei and almost completely covered by endothelium. The body of the cusp was composed of dense collagenous fibrous tissue showing areas of fibrinoid degeneration and increased cellularity in some areas. The valve ring was heavily vascularized. Other areas showed fragmentation of the collagen. A small wedge of myocardium, included with the section, revealed focal necroses of myocardial fibers which were replaced by foci of reticulum cells, lymphocytes and degenerating polymorphonuclear neutrophiles. The aortic cusps showed extensive collagenous thickening. The blood vessels of the valve ring were thickened. There was an atypical Aschoff body in the adventitia of the aorta and numerous scattered Aschoff-like cells with large nuclei and abundant basophilic cytoplasm. Sections of the myocardium of the auricles and ventricles

revealed diffuse interstitial fibrosis and focal cell accumulations composed of polymorphonuclear neutrophiles, lymphocytes and reticulum cells. Only one Aschoff body was observed. The intima of the medium sized vessels was thickened and there was extensive perivascular fibrosis.

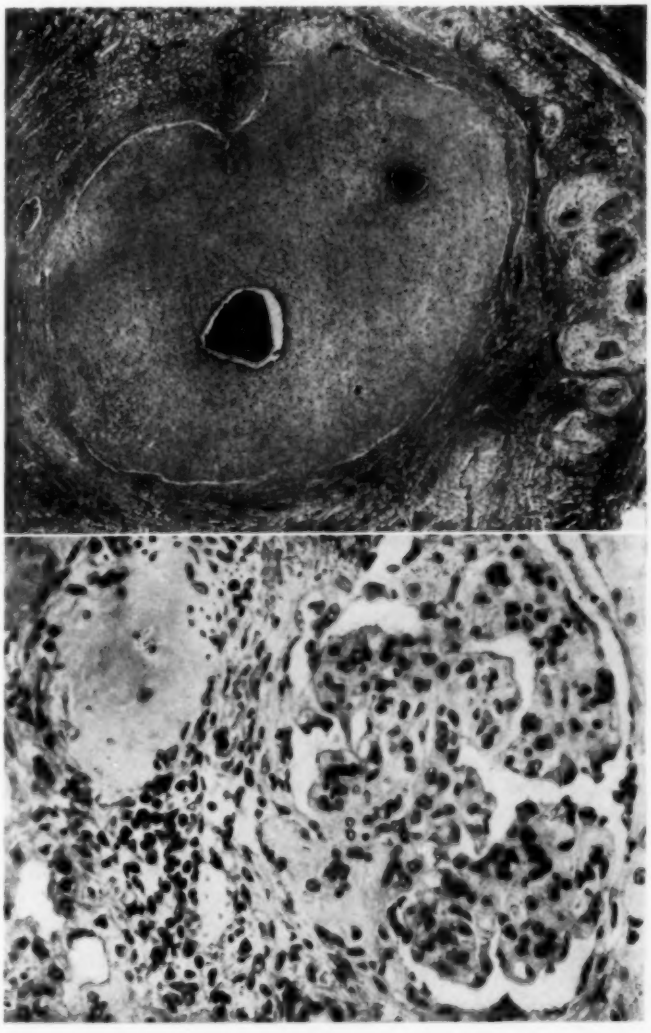

FIG. 3. (*Above*) Case 1. Interlobular renal vessel showing endarteritis. Almost complete obliteration of lumen by fibroblasts. Two canalized channels persist.
FIG. 4. (*Below*) Case 2. Necrosis of vasa afferentia. Degenerative and inflammatory changes in glomerulus.

Both pericardial layers were greatly thickened and adherent owing to dense heavily vascularized granulation tissue within the deeper layers. The more superficial layers were composed of heavy accumulations of inflammatory cells, polymorphonuclear neutrophiles, plasma cells, reticulum cells, lymphocytes and large Aschoff-like cells. These were embedded in thick masses of fibrin which was quite vascu-

larized. Organization of the superficial layers had begun and calcium masses were evident. Bacterial stains of the cardiac verrucae and pericardium were negative.

Kidney: About 60 per cent of the vasa afferentia, either in their extracapillary or intracapillary portions, or both, were transformed into fat free hyaline masses in which all cellular outlines were lost. Similar changes were observed in several portions of the capillary loops of nearly all glomeruli. In these the intima was swollen, endothelial cell outlines were indistinct, and the lumina were more or less devoid of red cells. Impaired circulation of red cells was as pronounced as the changes in the vasa afferentia. About 20 per cent of the glomeruli showed proliferation of the parietal layers of Bowman's capsule forming epithelial crescents, cellular or hyaline. Many showed adhesions between two capsular layers. Other tufts revealed varying degrees of collapse, fibrosis and hyaline changes. Some were shrunken and completely atrophic. Some of the necrotic vasa afferentia were invaded and surrounded by inflammatory cells (figure 4).

The epithelium of the entire tubular system showed degenerative changes, and there was a mild interstitial inflammatory cell infiltration localized to the cortex. The pelvis of the kidney was not inflamed.

Histological diagnoses: Chronic and acute valvulitis and myocarditis, rheumatic; fibrinous and fibrous pericarditis; focal glomerulitis and multiple renal arteritis.

Case 3. A young male with multiple arthritis and myocardial decompensation caused by rheumatic heart disease. Terminal uremia. Postmortem examination revealed rheumatic valvulitis, pericarditis and myocarditis with Aschoff bodies. Blood and vegetations were bacteria free. Focal glomerulitis and arteritis.

Clinical history: W. R., age 27, white male, machinist, was admitted to the hospital on May 29, 1937. His complaints were chills and fever, joint pains and shortness of breath for four days prior to admission. In November 1936, he had suffered a severe attack of acute arthritis involving both ankles and knees and was kept in bed at home for three weeks. From this he completely recovered. Since that time he suffered recurrent episodes of pains in various joints and had to stay in bed for three or four days at a time up to the present admission.

Examination revealed an acutely ill, pale and undernourished male breathing with difficulty. Temperature was 101.2° F. Respirations were 30 per minute. The pulse was rapid and completely irregular, with varied rate. Apical systolic and diastolic murmurs were noted. The heart was enlarged to the left. The liver was enlarged 2 fingers' breadth below the costal margin. The spleen was just palpable. The elbows, shoulders and knees were slightly inflamed. The skin over these joints showed erythematous macular lesions. A diffuse purpuric rash was noted later and many "white centered" petechiae. The patient had many hemoptyses of small amounts of bright red blood. Blood pressure was 104 mm. Hg systolic and 87 mm. diastolic.

Roentgenographic examination of the chest showed hilus markings on the left side to be considerably increased and the cardiac shadow enlarged on both sides. Electrocardiogram revealed "regular sinus rhythm and partial A.V. heart block."

Severe hematuria was noted on frequent urinalyses, the urine being bloody on gross and microscopic examination. No casts or pus cells were noted. Peripheral erythrocytes numbered 4 million per c.c. Leukocytes were 14,800 with 89 per cent polymorphonuclear neutrophiles.

Blood chemical tests revealed the total non-protein nitrogen to be 208 mg. per 100 c.c. with urea 121 mg. and creatinine 7.5 mg. per 100 c.c. Two blood cultures were sterile.

Temperature ranged between 98.8° and 102° F. The patient became increasingly dyspneic, cyanotic and edematous. The penis became enormously swollen, which condition was attributed to thromboses within the corpus cavernosum. On June 2, the "patient's back became suddenly covered with showers of white centered pe-

techiae." Severe anasarca developed. The patient rapidly went into deep coma and death occurred on June 2, 1937, five days after admission.

Clinical diagnoses: Chronic rheumatic endocarditis with terminal bacterial endocarditis; multiple pulmonary and renal infarction.

Postmortem examination (summary): There was severe anasarca. Scattered throughout both lungs were numerous firm red areas, more or less rectangular in shape, which were interpreted as infarcts. The heart weighed 350 gm. The pericardium was thin and translucent throughout except for the presence of numerous small, subpericardial hemorrhages. Several hemorrhages were present beneath the endocardium of the left ventricle. A small segment of the posterolateral endocardium of the left auricle was elevated, opaque and nodular. The cavities of the auricles and ventricles were slightly dilated, but the muscular walls were not significantly increased in thickness. The cusps of the aortic, tricuspid and mitral valves showed mild sclerosis but no significant deformities. On the ventricular aspect of the anterior cusp of the mitral valve, along the line of closure, was a continuous row of firm, small, grayish verrucae. Smears and culture of this lesion failed to reveal the presence of bacteria. The coronary arteries showed no changes.

Significant lesions in the abdominal cavities were limited to the kidneys. These organs were swollen, each weighing 200 gm. The cortical surfaces showed numerous petechial hemorrhages. No gross scarring or infarctions were present. The spleen weighed 100 gm. and showed no infarctions.

Anatomical diagnoses: Chronic cardiovalvular disease, rheumatic with acute mitral valvulitis; acute diffuse glomerulonephritis; multiple pulmonary infarctions.

Microscopy: Sections of the anterior mitral cusp showed a diffuse valvulitis throughout. The cellular infiltration was most predominant in localized areas, and consisted of reticulum cells, polymorphonuclear neutrophiles, intact and necrotic, and occasional plasma cells and lymphocytes. There was some palisade formation along the free border of the cusp where the superficial reticulum cells were arranged at right angles to the long axis of the cusp. Typical Aschoff bodies were present deep within the fibrosa and small polypoid masses formed typical verrucae capped by platelet thrombi, which arose from the ruptured endocardium along the closure line. Stains for bacteria were negative. In some areas the superficial surface of the cusp showed necrosis with a central acellular hyaline mass, surrounded by degenerated polymorphonuclear neutrophiles and reticulum cells. Other portions of the cusp revealed fibrinoid areas. The auricular myocardial wedge was heavily vascularized and cellular. Arising from the endocardium within the sinus pocket were small elevations composed of stellate reticulum cells capped by platelet thrombi. There was a diffuse valvulitis of the aortic cusps less marked than the mitral.

The endocardium of the proximal portion of the pulmonary artery was thickened by the accumulation of acellular pink staining hyaline or fibrinoid material. The adventitia of this vessel showed a considerable cellular infiltration, plasma cells, polymorphonuclear neutrophiles and atypical Aschoff cells.

Typical rheumatic verrucae were present in a section removed from left auricular endocardium. In some areas there was an intense cellular infiltration within the subendocardial tissues, but no bacteria could be demonstrated.

All of the renal glomeruli showed more or less alterations, affecting chiefly the capillary loops which revealed numerous pink staining acellular hyaline masses, partially or completely occluding the lumina of the capillaries. This lesion was partial in some glomeruli, massive in others. Many glomeruli showed an increase of nuclei within uninvolved portions of the tufts, or fibroblastic proliferations, recent or old, forming epithelial crescents. Endothelial and epithelial nuclei were more or less swollen, with granular degeneration. The size and contents of Bowman's capsule varied. In some glomeruli this was dilated and empty or contained a few inflam-

matory cells and erythrocytes. In others the space was obliterated by fibrous proliferations originating in the capsule (figure 5). Some of the vasa afferentia showed an arteritis of the inflammatory type with necrosis of their walls and cellular infiltrations. There were mild inflammatory cell interstitial infiltrations. The tubules were dilated and many packed with erythrocytes. Stains for bacteria were negative.

Microscopical diagnoses: Rheumatic valvulitis, myocarditis and pericarditis; multiple glomerular necroses with focal glomerulitis.

Case 4. Young male with signs and symptoms of acute rheumatic carditis and arthritis. Blood cultures were sterile. Postmortem examination revealed acute rheumatic pericarditis and valvulitis, bacteria free, without valvular deformity. Focal necroses of vasa afferentia and glomeruli. Acute arteritis.

Clinical observations: G. P., aged 27, a shipping clerk, was admitted to the hospital on January 17, 1940, because of precordial pain, weakness, fever, pain and swelling of the wrists. The patient had had rheumatic fever with multiple joint swellings at age of 11, was kept in bed for six weeks, and recovered fully. Since that time he had been quite well and "athletic" until two days before admission when his right wrist joint became swollen followed by similar changes in his left arm.

Examination revealed an acutely ill, pale young man, sweating profusely, dyspneic and cyanotic. Temperature was 104° F. Pulse was 140 per minute, completely irregular. Respirations were 30 per minute. His right ankle joint, the small joints of the feet and hands, and both knee and elbow joints were acutely inflamed and painful.

The heart was enlarged with diffuse heaving impulse. The sounds were of poor quality. A soft systolic murmur was audible at the apex. The lungs were congested.

Electrocardiographic tracing revealed sinus tachycardia. Repeated blood cultures were sterile. Urinalysis showed moderate albuminuria and 3–4 red cells per low power field with a similar number of pus cells. Erythrocytes numbered 3,700,000 with hemoglobin of 80 per cent. Leukocytes were 35,000 with 80 per cent polymorphonuclear neutrophiles. Blood chemical tests were within normal limits. Wassermann reaction was negative.

The temperature continued high, varying between 102 and 105° F. Conjunctival petechiae were noted. Pericarditis developed. The patient was placed in an oxygen tent but died on January 21, 1940, four days after admission.

Clinical diagnoses: Acute rheumatic myocarditis, pericarditis and endocarditis; rheumatic polyarthritis; acute bacterial endocarditis (?).

Postmortem examination (summary): The right pleural cavity contained about 100 c.c. of clear fluid. There were recent pleuropericardial adhesions. The lungs showed severe congestion with numerous ecchymoses covering the visceral pleurae. There was marked fibrinous and fibrous adhesive pericarditis. The pericardial sac contained about 50 c.c. of turbid yellow fluid. The heart was only slightly enlarged. All chambers were mildly dilated. On the line of closure of the aortic, mitral and tricuspid valves were identical small, rather flat verrucae forming a discontinuous line. There was no significant degree of scarring of the cusps. The chordae tendineae were not thickened. Smears of the valvular vegetations and of the pericardial exudate revealed no organisms.

The spleen weighed 225 gm., was congested, and showed no infarction.

The kidneys weighed 330 and 320 gm., were swollen with tense capsule. Cut section revealed marked edema and petechial hemorrhages.

Anatomical diagnoses: Acute rheumatic pancarditis; acute glomerular nephritis.

Microscopy: Most of the glomeruli were well preserved and showed only mild parenchymatous degeneration of endothelial and epithelial cell elements. In about 10 per cent there were necroses of the vasa afferentia in their intra- or extraglomerular portions. This consisted of an accumulation of pink staining acellular

material which more or less completely obliterated their lumina. Other glomeruli showed similar necrosis of varying degree within a portion of their loops, the remainder of the capillary being uninvolved. Some glomeruli were completely infarcted.

A few medium sized arteries revealed severe necrosis and arteritis, the entire wall being eroded by inflammatory cells.

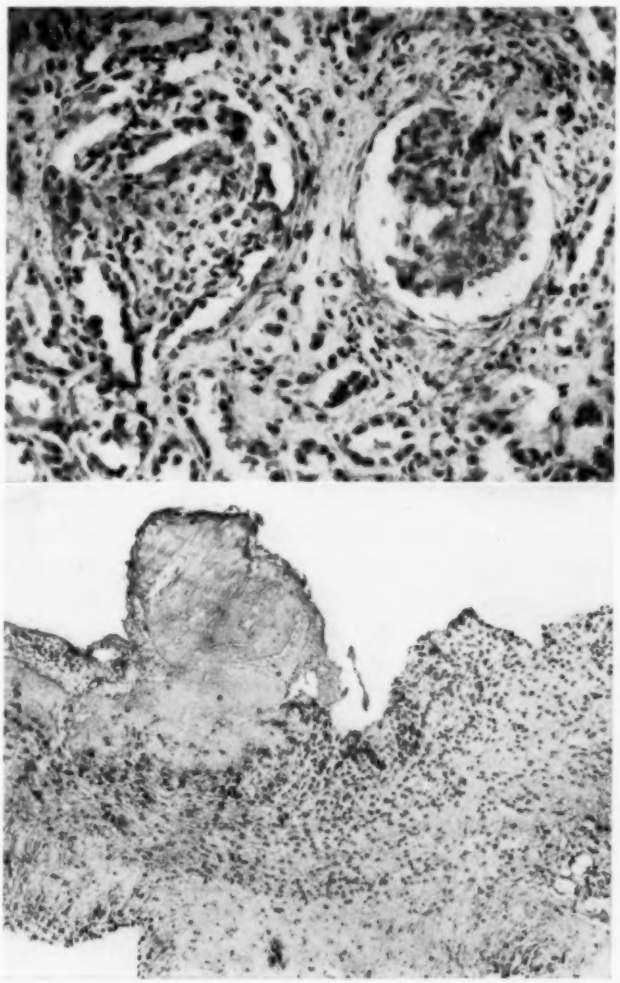

FIG. 5. (*Above*) Case 3. Inflammatory and degenerative changes in glomeruli. Hyaline necrosis of vasa afferentia.
FIG. 6. (*Below*) Case 4. Diffuse valvulitis. Hyaline verruca on aortic valve cusp.

The collagen of the aortic valve ring and cusp was vacuolated and fragmented. The spongiosa of the ring was inflamed with increased capillaries and cells. The entire cusp showed increased cellular exudation chiefly reticulum cells, plasma cells, a few polymorphonuclear neutrophiles, numerous Aschoff-like cells and one Aschoff body underneath a hyaline or eosinophilic surface thrombus near the line of closure. Valvulitis of the mitral valve was similar though of greater intensity. Vessels of the

myocardium were surrounded by rings of fibrous tissue, but no Aschoff bodies were evident.

Sections of the valves and pericardium stained for bacteria were negative.

Microscopical diagnosis: Acute rheumatic valvulitis and pericarditis; multiple focal necroses of the vasa afferentia and glomerular capillaries; acute arteritis of medium sized renal vessels.

Comments on Cases 2, 3 and 4. The clinical course of this group was consistent with the symptomatology and signs usually associated with severe rheumatic heart disease which was the diagnosis in cases 2, 3 and 4. In all cases repeated blood cultures were sterile. Electrocardiography revealed increased A.V. conduction time in cases 2 and 3.

The gross anatomical and histological lesions in all were typical of rheumatic heart disease.[19, 20, 21] Although the glomerular lesions of cases 2 and 3 resembled the focal embolic glomerular nephritis of Löhlein,[22] described in subacute bacterial endocarditis, this author has described similar changes in rheumatic renal disease.[23]

Other features occurred which led the clinicians to consider the additional presence of subacute bacterial endocarditis in cases 2 and 3 and acute bacterial endocarditis in case 4, despite repeatedly negative blood cultures. Severe nitrogen retention was present in cases 2 and 3. All showed severe hematuria. Case 3 presented a severe erythematous skin rash and petechiae, some of which were described as "white centered." Similar erythematous rashes and petechiae have been described in uncomplicated rheumatic fever.[9] Necropsy disclosed extensive renal arteritis and glomerular lesions sufficient to explain the high grade renal insufficiency present in cases 2 and 3. Despite the demonstration at necropsy of similar changes in the kidneys of case 4, although less severe in intensity, blood chemical tests were within normal limits. The presence of pericarditis, the absence of extensive visceral infarction, and the sterile verrucae and blood militate against the postmortem diagnosis of bacterial endocarditis in this case.

Discussion. Although clinical evidence of renal involvement is seldom observed in rheumatic fever, there have been numerous observations of the frequency of glomerular and vascular changes observed at necropsy.

Klotz[24] was one of the earlier writers to emphasize the frequency of visceral involvement. In the kidney he described a non-suppurative perivascular infiltration around the interlobular arteries, with healing by fibrosis and the production of a granular contracted kidney.

Fahr[25] described cases in which renal disease followed rheumatic infection and states that rheumatism may be an etiological factor in some cases of malignant nephrosclerosis. Klinge[12] studied renal lesions in cases dying during the active stage of rheumatic fever. In single sections he found either a focal nephritis of the Löhlein type or a subacute diffuse glomerulonephritis; in serial sections numerous periarterial and perivenous foci of epithelial cells, lymphocytes and some polynuclear or nodular formations involving the entire wall and protruding into the vascular lumina. Rössle[26]

used the term "tuberculoid periarteritis nodosa" to describe a periarterial granulomatous lesion with giant Aschoff bodies, found in the kidney and heart, in a case of rheumatic fever.

Nephritis may precede, occur simultaneously, or follow the onset of rheumatic manifestations. Glomerular lesions are usually of the focal embolic type or acute diffuse glomerulonephritis may occur.

In case 1 of Salvesen's series [8] acute polyarthritis was the first evidence of the onset of rheumatic fever which was followed by urinary changes, renal insufficiency and uremia. With the onset of the latter the joint symptoms disappeared but returned when the uremic syndrome had abated. In case 4 of the same author acute nephritis occurred immediately after the onset of acute rheumatic fever. The nephritis progressed to the chronic stage over a course of three years. Uzan's [3] case developed hypertension and renal insufficiency soon after the onset of rheumatic fever with arthritis. The patient presented a terminal uremic syndrome. In the case of Bernard [5] high fever, lumbar pain, oliguria with albuminuria, hypertension and nitrogen retention preceded joint symptoms and other typical rheumatic manifestations by an interval of 27 days.

Considerable controversy has arisen concerning the nature of the renal lesions in rheumatic fever. Endarteritic changes in the large and small vessels are generally assumed to be caused by the circulating rheumatic [27] toxin or virus. Löhlein in his first paper [22] stated that the focal glomerular lesions were the result of capillary thromboses but later [23] attributed them to dislodged particles from the heart valves causing minute glomerular embolization. Bell [11] believed that focal lesions are associated chiefly with subacute bacterial endocarditis, although he found them in three out of 104 cases of rheumatic fever in which the kidneys were studied. He stated that the lesion is not specific and that the duration of the endocarditic infection is important in causation and that focal embolic lesions are rare in cases of less than six weeks' duration. Longcope [28] also denied the specificity of these lesions and stated that they may be caused by inflammatory factors of diverse etiology.

Summary

1. In a series of 3000 postmortem examinations three cases showing focal glomerulitis and arteritis and one case with diffuse obliterative renal vascular disease were found in patients with active rheumatic heart disease and Aschoff bodies in the myocardium.

2. In two cases renal involvement was severe and renal insufficiency was the most prominent feature in the clinical symptomatology.

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THE ULTIMATE EFFECT OF PREGNANCY ON RHEUMATIC HEART DISEASE*

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THE immediate risk of pregnancy in women with rheumatic heart disease has been admirably surveyed by Hamilton and Thomson,[1] but the ultimate effect of the circulatory load of repeated pregnancies and the hardships of motherhood upon a handicapped heart has not been subjected to the same thoroughgoing analysis. These authors expressed the opinion, based on clinical impression, that there was no strong evidence pointing toward an unfavorable late effect of pregnancy on the course of rheumatic heart disease. They had no statistical proof to offer, and, in fact, doubted that such proof could be obtained in a practical way. We would be among the first to admit that a study of this kind is fraught with difficulties, for there are numerous known, as well, perhaps, as other unknown factors which can, and do, affect the mortality among patients with rheumatic heart disease. We have refused, however, to be daunted by the difficulties of the issue and have particularly tried to profit by the errors which have been evident in the published reports of others who have attacked the problem.

The average age at death of patients with rheumatic heart disease has been investigated by French and Hicks,[2] Gilchrist,[3] Reid,[4] Scott and Henderson,[5] and Jensen.[6] One or more objections can be raised to all these studies, the more important of which, it seems to us, are: (1) the inclusion of cases that died of causes other than congestive heart failure, (2) the small number of cases reported,[4] and (3) the use as controls of patients who may have been too ill and died at too early an age to have borne children.

It seemed to us that if pregnancy had any delayed effect on the course of rheumatic heart disease it would be reflected in the age at death from congestive heart failure alone and not from extracardiac causes or from such accidents as bacterial endocarditis or embolism. Furthermore, we considered it essential to eliminate those cases with complications lethal in themselves, even though congestive heart failure may have been a contributory cause of death. We felt also that inclusion of patients dying of congestive failure precipitated by, or during the course of pregnancy was not consistent with the purpose of the study.

In addition to the age at death it seemed that a further indication of the strain of childbearing might be obtained by a comparison of the heart weight at autopsy among parous and nulliparous women with the same type and approximately equal degree of valvular deformity.

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In order to keep the group as homogeneous as possible only one stratum of society is represented. All the patients were charity cases on the wards of the Massachusetts Memorial Hospitals, Boston City Hospital, and Massachusetts General Hospital * for the years 1930 to 1941 inclusive. We have included only patients who lived to at least the beginning of the reproductive period, which we arbitrarily set at 18 years of age.

Clinical Data

One hundred and three patients having had one or more pregnancies and 49 patients having had no pregnancies, who conformed to the criteria set forth above, were available for study. The average age at death for the patients who had borne children was 43.7 years as compared to the average age of 39 years for those who had never been pregnant (table 1). It hardly

Table I

Average Age at Death from Congestive Heart Failure of Women with Rheumatic Heart Disease According to Antecedent Pregnancies, First, Including All Cases Who Had Reached the Age of Childbearing, and Second, Including Only Those Who Survived to Approximately the End of the Childbearing Period.

		No. Cases	Average Age at Death
18 years of age or over	Parous	103	43.7
	Nulliparous	49	39.0
40 years of age or over	Parous	68	51.5
	Nulliparous	22	49.7

seemed likely that childbearing had actually increased life expectancy and it was found on further analysis that a large proportion of the nulliparous patients had died early in the reproductive period. Eighteen, or 37 per cent, of all the nulliparous women died between the ages of 18 and 29. In the same age period only eight (7.7 per cent) of the patients who had borne children succumbed to heart failure. The inference that severe illness and early death had probably played a part in prohibiting pregnancy seemed fairly plain. Therefore, we eliminated all patients who had not survived to the end of the reproductive period which was arbitrarily set at 40 years. Elimination of the younger group also tends to minimize the troublesome factor of active rheumatic infection as a cause of mortality. As far as is known, pregnancy bears no significant relation to recurrences of rheumatic infection.[1]

There were 22 patients surviving to the age of 40 years who had never been pregnant. The average age at death (table 1) was 49.7 years, with a range of 40 to 61 years. Sixty-eight of the patients who had had pregnancies survived to 40 years and their average age at death was 51.5 years,

* We wish to take this opportunity to thank the administrative officers of the Boston City and Massachusetts General Hospitals for making their records available to us, and to Dr. Paul D. White and Dr. James M. Faulkner through whose kindness the records of the Massachusetts General and Boston City Hospitals were obtained.

with a range of 40 to 84 years. For practical, as well as statistical purposes, these figures are identical. The groups were further subdivided according to the presence or absence of auricular fibrillation but the number then became too small to be of significance and, therefore, have been omitted from the table. Such subdivision did not, however, materially alter the results.

When only the cases surviving to the age of 40 years are used the control, or nulliparous, group becomes small. There is a further objection to using nulliparous patients as a control group because of the possibility that only women in good health marry and have children.[3] A priori it seems unlikely that the patients would survive to 50, 60, or more years, and yet have been too ill from 18 to 40 to have had pregnancies. Nevertheless, it seemed desirable to have another control group and the use of male patients for such a purpose naturally suggested itself.

TABLE II

Average Age at Death from Congestive Heart Failure in Subjects with Rheumatic Heart Disease According to Sex, Valves Affected, and Presence of Auricular Fibrillation. Two age groups are considered, one including all patients 18 years of age or over, the other including only those 40 years or over. The female group includes both parous and nulliparous women.

Males

	18 Years or Over				40 Years or Over			
	All Cases		With Aur. Fib. Only		All Cases		With Aur. Fib. Only	
	No. Cases	Av. Age	No. Cases	Av. Age	No. Cases	Av. Age	No. Cases	Av. Age
Mitral alone	61	40.8	30	43.1	32	49.7	18	51.9
Mitral and aortic	76	38.8	36	43.8	34	50.5	21	52.0
Females								
Mitral alone	82	42.1	54	44.0	68	50.0	34	50.4
Mitral and aortic	51	42.2	24	42.2	30	49.3	13	49.9

Accordingly, the average ages at death from congestive heart failure for males and females of a comparable age group, i.e., 18 years or older, were computed and are shown in table 2. Before one can confidently use males as a control group some pertinent questions must first be answered. For example, it is generally known that the relative incidence of valves affected differs in the two sexes and that the greater number of male patients with aortic valvular disease, either alone or in combination with mitral disease, might introduce a considerable error. Table 2 shows the average age at death according to sex and valves affected. It will be seen that for either sex there is no significant difference whether the mitral valve was affected alone or in combination with the aortic valve. Males with aortic disease alone lived a significantly longer time than those with mitral or mitral and aortic disease. In large part this is due to the inclusion of a few old men with

calcific aortic stenosis. There are those who doubt that such a lesion is always of rheumatic origin and for this reason as well as because it occurred but rarely in the female group these patients were eliminated from consideration. The presence of auricular fibrillation has also been taken into account in table 2. It is readily apparent from this table that there is no sex difference in the average age at death from congestive heart failure and that the valves affected or the presence of auricular fibrillation are not factors of importance in determining the age at death from congestive failure.

TABLE III

Average Age at Death from Congestive Heart Failure in Subjects with Rheumatic Heart Disease

		No. Cases	Av. Age at Death
18 years or older	Nulliparous	49	39.0
	Para IV or more	46	46.2
	Males	137	39.8
40 years or older	Nulliparous	22	49.7
	Para IV or more	34	49.8
	Males	66	50.1

The use of males as a control group, therefore, appears justifiable. It is evident from comparisons of the average ages at death in tables 1 and 2 that women who have borne children do not die sooner than either nulliparous women or males. All of the differences in average ages have been subjected to statistical analysis and have been found not to be significantly different.

It seemed that perhaps the inclusion of a fairly large number of patients (40 per cent) in the pregnant group who had only one or two pregnancies might be confusing the issue and that a more striking difference could be

TABLE IV

Average Age at Death According to Number of Pregnancies, Exclusive of Patients Dying Before 40 Years of Age

No. of Pregnancies	No. Cases	Average Age
0	22	49.7
I	10	60.8
II	13	46.8
III	9	44.5
IV	11	48.0
V	7	48.3
VI	5	54.6
VII	3	46.6
VIII–XI	10	51.5

shown by comparing the average age at death for patients who had had four or more pregnancies with patients who had had no pregnancies. This was done and the results are shown in table 3. There were 46 patients who had had four or more pregnancies and the average age at death was 46.2 years as compared to 43.7 years for all patients with pregnancies and to 39 years for the patients who had had no pregnancies. This probably means only that the longer the patients in this series lived the more pregnancies there were likely to be. Again excluding the patients who died before the age of 40

years the average age at death for 34 patients with four or more pregnancies was 49.8 years, with a range of 40 to 72 years, as compared to 49.7 years for the patients who had had no pregnancies. The male patients are also included in this table as a control group. It will be seen that the average age at death, when all patients 18 years or older are considered, is almost exactly the same for males and for nulliparous women but is considerably older for the women having had four or more pregnancies. When only the patients who survived to at least 40 years are considered the average age at death is practically identical for nulliparous women, parous women, and males. Thus even multiple pregnancies cannot be held accountable for any reduction in the average age at death. This is further shown in table 4 where the average age at death according to the number of pregnancies is shown.

Postmortem Data

Comparison of the average heart weights at autopsy of patients in whom *mitral deformity was the only cardiac defect* is shown in table 5. The average weight of the hearts of 27 parous women was 482 grams, with a range of 300 to 900 grams. The average heart weight for 16 nulliparous women was 476.2 grams, with a range of 300 to 660 grams. Since the

Table V

Autopsy Data on Patients in Whom Rheumatic Disease of the Mitral Valve Was the Only Significant Cardiac Defect. All patients died of congestive heart failure

	No. Cases	Av. Circum. Mitral	Av. Heart Weight
Nulliparous	16	5.5 cm.	476.2 grams
Parous	27	6.1 cm.	482.0 grams

degree of valvular deformity, as measured by the average circumference of the mitral valve, is essentially the same for both groups, one can conclude that childbearing did not produce cardiac hypertrophy out of proportion to that found in nulliparous women. Whatever increase in cardiac work accompanying childbearing there may be, it is not reflected in the degree of cardiac hypertrophy at autopsy.

Table 6 compares the heart weight of individual cases, alike with respect to age and degree of valve deformity, but different in regard to the number of pregnancies. It appears that heart weight is absolutely independent of the number of pregnancies for, in each instance, the weight of the heart in cases of comparable age and degree of valve deformity is not significantly increased by multiple pregnancies. Instances can undoubtedly be found in which the weight of the heart of women having had multiple pregnancies is much greater than in cases of comparable age and degree of valvular defect who have not borne children, but it seemed of interest, and perhaps of importance, that such an instance was not found in this series. The table is

TABLE VI

Comparison of the Heart Weight at Autopsy of Patients in Whom Rheumatic Disease of the Mitral Valve Was the Only Significant Cardiac Defect, and in Whom Congestive Failure Was the Cause of Death. Each pair of cases is similar in regard to age and degree of mitral valve deformity but dissimilar in the matter of pregnancies. It is evident that multiple pregnancies are without influence on the degree of cardiac hypertrophy.

Age at Death	Circumference of Mitral Valve	Heart Weight	No. Pregnancies
60	4.8 cm.	440 gm.	none
59	4.5 cm.	400 gm.	10
49	3.5 cm.	420 gm.	none
49	4.0 cm.	480 gm.	9
58	6.5 cm.	550 gm.	1
58	6.8 cm.	585 gm.	10
54	4.0 cm.	540 gm.	none
54	4.5 cm.	430 gm.	"several"
41	6.0 cm.	590 gm.	none
42	4.5 cm.	460 gm.	11
58	8.0 cm.	650 gm.	none
59	7.3 cm.	460 gm.	5

also of interest in showing that a large number of pregnancies is not necessarily incompatible with as long a life as was enjoyed by nulliparous women with an equal degree of valvular deformity.

Furthermore, the average heart weight does not increase with increasing number of pregnancies as can be seen in table 7. The degree of valvular deformity is essentially the same for all the groups and the difference in average heart weight is not statistically significant.

TABLE VII

Average Heart Weight in Patients with Rheumatic Heart Disease Who Had Died of Congestive Heart Failure and in Whom Mitral Valve Deformity Was the Only Cardiac Defect. The differences in heart weight are not statistically significant.

Parity	No. Cases	Av. Circum. Mitral Valve	Av. Heart Weight
Nulliparous	16	5.4	476.2
I–II	9	5.2	530.5
III–IV	8	6.6	488.0
V–XI	9	6.5	520.0

DISCUSSION

Our results are in accord with those of others who have made similar studies [3, 4, 5, 6] with regard to the lack of evidence pointing toward a deleterious *late* effect of pregnancy in patients with rheumatic heart disease. Objections have been raised to the use of the age at death as a criterion for such a possible effect. McIlroy and Rendel [7] noted a high proportion of

multiparae in those patients with poor cardiac reserve and stated that this "emphasized the fact that multiple pregnancies tend to lower the cardiac efficiency permanently." There is no reason apparent to us why women who have borne children might live longer after diminished cardiac reserve or actual failure has made its appearance than nulliparous women. Indeed, the pressure of maintaining a household might well be expected to have the reverse effect.

The duration of the heart disease may well be a factor of greater importance than the age at death. One cannot be certain, for example, that some of the pregnancies had not occurred before the onset of the heart disease. Information on this point can only be obtained by following a large group of patients from the time of first infection until death. Attempts have been made [6] to estimate the duration of the heart disease on the basis of historical data but in so doing two assumptions must be made. First, it must be assumed that heart disease was caused by the first remembered attack of rheumatic fever and not subsequent attacks or continued low grade activity of the infection. Secondly, it must be assumed that the first remembered attack was not preceded by forgotten or unrecognized rheumatic infection. Both assumptions are unwarranted and may lead to erroneous conclusions. Because of this source of error no attempt was made to estimate the duration of the heart disease, or the effect of pregnancy on it, in this study.

Gilchrist [3] has emphasized the dangers inherent in using nulliparous women as a control group owing to the following considerations: (*a*) only the more physically fit marry; (*b*) of those who marry, only the fitter have pregnancies; and (*c*) women with large families necessarily have lived longer. We believe we have largely obviated these objections by considering only those patients who had survived to approximately the end of the reproductive period. As stated previously, it seems unlikely that the nulliparous women who survived, on the average, 10 years after the end of the child-bearing age could have been in such a delicate state of health all their lives as to preclude pregnancy. Furthermore, the apparent reliability of the use of males as a control group and the absence of any sex difference in the average age at death strengthens the argument that the groups are indeed comparable.

Cardiac Hypertrophy. If one believes, with most students of the subject, that cardiac hypertrophy may well prove to be the eventual undoing of the patient with cardiac disease then it is logical to assume that the more work the heart is required to do the greater will be the hypertrophy and the sooner the breakdown will occur. It has been shown that athletes and laborers tend to have somewhat larger hearts than men leading sedentary lives and that very active animals have relatively heavier hearts than less active members of the same species.[8] It seems to us that the question comes down to one of the comparability of the difference of cardiac work involved between the bearing and rearing of children and a normal, active, childless life with the difference between the activity of the wild hare and its more leisurely cousin, the domesticated rabbit. Both *a priori* reasoning and the results of this study

indicate that childbearing cannot be considered to have that degree of importance. If this is true, it has implications which carry the principle beyond the subject of pregnancy and into the every day lives of all patients with rheumatic valvular disease. It gives support to Mackenzie's belief that activity does no harm to the patient with valvular disease as long as symptoms do not result. The applicability of this general rule is far less certain in such forms of heart disease as syphilitic, hypertensive, or coronary disease. It is certainly not to be followed during acute inflammatory disease of the heart.

We do not wish to leave the impression that we think it is desirable to let down the bars completely and consider the course of rheumatic heart disease as entirely beyond control. This is probably poor treatment and certainly poor psychology from the victims' point of view. We believe that every patient with rheumatic heart disease should lead a well regulated life, but that there are limits beyond which one is not justified in going on the basis of present knowledge. The denial of motherhood on the basis of possible future ill-effects appears to be an instance of ill-founded over cautiousness.

It hardly needs to be emphasized that the patient with rheumatic heart disease faces a definite *immediate* risk in pregnancy and that the results of this study apply only to those who have come safely through pregnancy and the puerperium. How much a natural process of selection may have been operative we have no way of knowing. It is probable that the patients who died of congestive failure during pregnancy or the puerperium are the ones most likely, had they survived, to show any tendency toward delayed unfavorable effects which might be present. For the present, at least, this must remain an imponderable question.

Summary and Conclusions

The average age at death from congestive heart failure is significantly older for women who have borne children than for those who have had no pregnancies when all cases 18 years of age or older are considered. This is accounted for by the fact that the nulliparous control group is not comparable to the parous group because of death early in the reproductive period of a large number of those who had not been pregnant.

When only those patients are considered who lived to approximately the end of the reproductive period, i.e., 40 years of age, there is no significant difference in the average age at death of the nulliparous or parous women. Furthermore, multiple pregnancies (four or more) cannot be shown to reduce the average age at death.

There is no significant difference in the average age at death for males and females with rheumatic heart disease whether the groups are considered as a whole or are subdivided according to the valves affected (exclusive of affection of the aortic valve alone) and the presence of auricular fibrillation. Accordingly, males can be used as a control group for parous women, thus obviating certain objections to the use of nulliparous women as controls.

Consideration of postmortem data did not reveal that the increased load of pregnancies and motherhood produced any appreciable increase in cardiac hypertrophy.

It is concluded, therefore, that pregnancy has no delayed deleterious effect on the course of rheumatic heart disease.

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STUDIES IN ACUTE MYOCARDIAL INFARCTION. I. THE CLINICAL PICTURE AND DIAGNOSIS*

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ONLY in the last decade has acute myocardial infarction been considered as Christian [1] thought it should be, "an easily diagnosable condition." Following the early excellent clinical descriptions by Herrick,[2] Levine and Tranter,[3] Wearn,[4] Gardinier,[5] and Hamman,[6] the medical profession began to realize that myocardial infarction was neither as rare nor as fatal as it was originally considered.

It seemed profitable to review the cases seen in a large general hospital and determine what progress had been made during the past decade in the diagnosis and treatment of acute myocardial infarction. The material presented includes every case of acute myocardial infarction admitted to the wards and private pavilions of Jewish Hospital, Philadelphia from 1929 to 1941.

Selection of Cases. During the period from January 1, 1929 to December 31, 1941, 508 cases were discharged or died with the final diagnosis of acute myocardial infarction. The great majority of these patients were admitted during the first 14 days of their illness, though some cases were included that did not enter the hospital until four or five weeks after the acute attack. With the exception of 15 cases which we felt had a typical clinical picture (friction rub, previous attack, etc.), no case was included in this series unless it presented diagnostic electrocardiographic or necropsy changes. The use of electrocardiographic chest leads was begun at this hospital shortly after their recommendation by Wolferth and Wood and their associates.[7, 8, 9] Every electrocardiogram was reviewed by one of us (S. B.), with consideration of the electrocardiographic patterns suggested by Levine,[10] Katz,[11] and Wolferth et al.[7, 8, 9] Using these rigid diagnostic criteria, a number of cases of sudden death on the surgical or medical wards were eliminated because necropsy was not done. Many cases of old infarction were not included because the electrocardiogram did not present evidence of a new infarction. In all 130 cases were excluded because they did not present sufficient clinical, electrocardiographic or postmortem evidence of acute infarction. There remained for consideration then, 378 cases of acute myocardial infarction.

The Clinical Syndrome. The predominance of myocardial infarction in the male has been a well recognized fact. As the condition became better recognized, more cases were found in women. Twenty-five per cent of our cases occurred in women, an incidence of three males to one female. This

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compares with the 3 : 1 ratio reported by Levine [12, 13] and by Master et al.[14] Willius [15] reported a 7 : 1 ratio in males as compared to females, and Conner and Holt [16] found as high as 85 per cent occurrence in men.

Our patients ranged from 27 to 89 years. In the last few years, more and more cases have been seen in younger individuals. Stroud [17] has seen a

TABLE I
Age Incidence by Decades

Age	Males			Females		
	No. Cases	Deaths	Per Cent	No. Cases	Deaths	Per Cent
20–29	1	0	0	—	—	—
30–39	7	0	0	2	1	50
40–49	67	17	25	9	1	11
50–59	96	31	31	21	8	38
60–69	81	42	52	41	21	51
70–79	29	14	48	17	9	53
80–89	2	1	50	5	3	60
Total	283	105	37.1	95	43	45.3

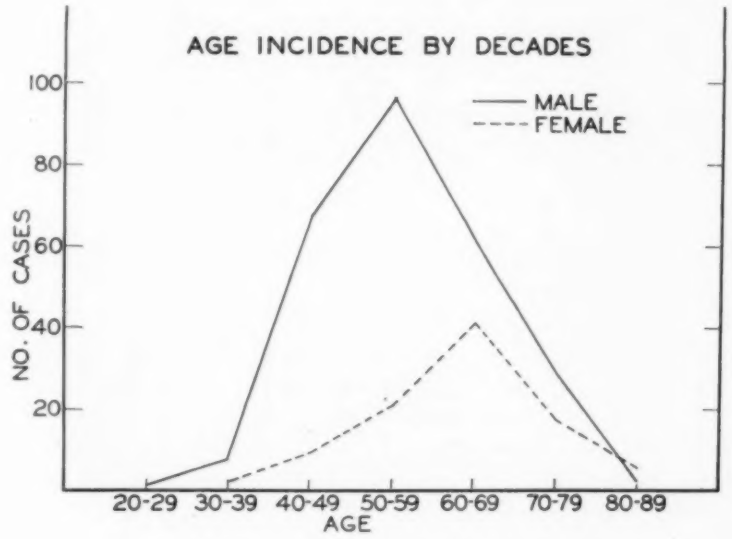

FIG. 1.

case in a man of 28; Levine [12] found one in a man of 24; and Doane [18] has seen an acute myocardial infarction in a young man of 22. Table 1 and figure 1 show the age incidence by decades in men and women. It is apparent, as many observers have emphasized, that the peak incidence in the female occurred at a later period. Not only did the attack occur later in life in women, but fatal cases in both sexes were apt to be older (table 2). We plan to discuss the factors influencing the immediate mortality of acute

myocardial infarction in another paper, but a consideration of tables 1 and 2 suggests that: (1) The younger individual has a somewhat better immediate prognosis; (2) the mortality is slightly higher in women; (3) the mortality increases with advancing years. Though these figures do not all prove to be statistically significant, they are so in accord with the data presented by other observers [18, 19] that they must be given some weight.

TABLE II

Average Age

	Males	Females
Recovered	55.3 yrs.	58.8 yrs.
Died	58.8 yrs.	65.0 yrs.
Total	56.7 yrs.	61.6 yrs.

The symptoms presented by a patient with acute myocardial infarction are well recognized. As seen in table 3 and figure 2, 90 per cent had pain, 76 per cent dyspnea, and 46 per cent cyanosis. Of late, there has been quite a good deal of discussion in the literature relative to painless myocardial infarction. In two widely discussed papers, Gorham and Martin [20, 21] quoted four reports on painless myocardial infarction, with percentages of cases without pain ranging from 38 per cent to as high as 61 per cent. Stroud and Wagner [22] recently reported that 13 of 49 cases had no pain. Gorham's cases included chronic as well as acute infarctions. Only five of their cases of acute in-

TABLE III

Symptoms and Physical Findings

	Male		Female		Total
	No.	Percentage	No.	Percentage	Percentage
Pain	256	91%	82	86%	90%
Dyspnea	213	75%	75	79%	76%
Cyanosis	134	47%	40	42%	46%
hock	50	18%	10	11%	16%
Vomiting	41	14%	10	11%	13%
Hypertension	73	26%	69	73%	37%
Fever	186	66%	62	71%	66%
Tachycardia	130	46%	49	55%	47%
Cardiac Failure	113	40%	55	62%	44%
Friction Rub	35	12%	10	11%	12%

farction alone had no pain. Wearn [4] long ago pointed out that the classical symptoms of acute coronary thrombosis may not appear when the occlusion occurs in the presence of myocardial insufficiency. Bean [23] noted pain in 72 per cent of 300 autopsied cases, but here again many of the cases were not acute. In contrast to these figures, Rosenbaum and Levine [19] found that but 3 per cent of acute infarctions were painless, Kennedy [24] 4 per cent, and Pollard and Harvill [25] 8.5 per cent. We believe that painless acute myocardial infarction is rare, and that some degree of pain will be present in about 95 per cent of cases. Pain was noted in 90 per cent of our cases,

and this is the minimum percentage that experienced pain. Detailed histories could not be taken on a number of cases that were admitted in extremis and promptly died. It is reasonable to expect that some of these patients also suffered pain.

A number of factors influence the physical findings present in these cases. Fever above 99° F. was present in 66 per cent of cases, and tachycardia above 100 in 47 per cent. In a better controlled group of cases that could be observed from the onset of their illness, the incidence of fever and

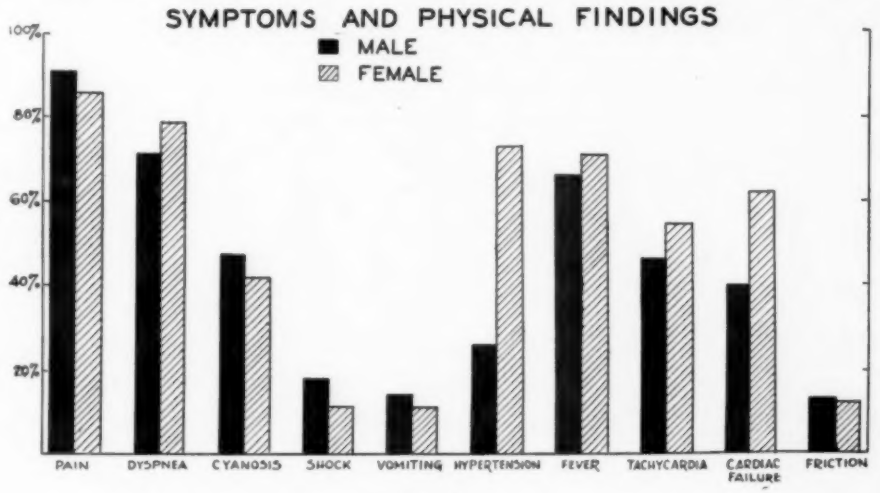

FIG. 2.

tachycardia probably would be a good deal higher. It must be remembered that some cases were admitted 10, 15 or 20 days after the onset of their illness, during which time the temperature and pulse might have returned to normal. Rosenbaum and Levine [19] found a rectal temperature above 100° F. in 93 per cent of cases. Shilleto, Chamberlain and Levy [26] in 50 cases observed from the onset of the acute attacks, reported fever in 100 per cent and tachycardia above 80 in 98 per cent. The incidence of the various physical signs varies with the detail with which they are sought. It is to be expected that those who are particularly interested in phases of this problem would be more apt to find a transient gallop rhythm or friction rub than a casual observer. Levine [12, 13] found gallop rhythm present frequently. In our series mention of a gallop rhythm being present was made but 22 times. Shilleto et al.[26] found a gallop present in 28 per cent, and a friction rub in 20 per cent. Rosenbaum and Levine [19] reported a friction rub in 16 per cent of their cases. In our series the incidence was 12 per cent. Friction rubs may be present for but a few hours, and unless diligently sought may be missed.

Two findings that become apparent after studying table 3 and figure 2, are, the more frequent presence of hypertension and cardiac failure in the female. These figures are statistically significant. It has long been known that

hypertension is a much more common precursor of myocardial infarction in the female than the male. It is a rarity to find an acute myocardial infarction in women without hypertension or diabetes, unless the woman is old enough to have severe atherosclerosis.

There are two factors that might explain the greater percentage of cardiac failure in the female. The first is the greater incidence of hypertension, which predisposes to cardiac failure. The second is the fact that acute myocardial infarction, on the average, occurs five years later in the female. We would expect that the older the individual, the greater is the possibility of cardiac failure developing.

TABLE IV

Diagnosis on Admission

Diagnosis	No. of Cases
Acute myocardial infarction	185
Angina pectoris	15
Coronary artery disease	43
Cardiac failure	57
Miscellaneous (all cases)	78
Pneumonia	12
Hypertension	9
Gall-bladder disease	7
Uncertain	5
Hemiplegia	4
For study	4
Peptic ulcer	3
Diabetes mellitus	3
G.I. malignancy	3
Grippe	2
Acidosis	2
Gastro-enteritis	2
Purpura, uremia, arteriosclerosis, pyelonephritis, ca. of prostate, Parkinsonism, hypernephroma, pneumothorax, diabetic coma, urethral stone, endocervicitis, lead colic, prostatic disease, fractured femur, hernia, anemia, ventricular fibrillation, bursitis, circulatory failure, bronchitis, appendicitis, erythema multiforme (one each)	22

In table 4 are listed the diagnoses with which these 378 patients were admitted. Only 50 per cent were admitted with a diagnosis of acute myocardial infarction, and 78 cases or 20 per cent had no diagnosis referable to the heart. Though an occasional case developed unexpectedly as a complication of a surgical procedure, it is apparent that the diagnosis of acute myocardial infarction can be a difficult one. Herrick [28] listed 28 conditions that must be considered in the differential diagnosis of this condition. Today the correct diagnosis is probably made much more frequently, for the constant emphasis upon acute myocardial infarction in the past decade has made physicians more "coronary thrombosis" conscious. The diagnosis should be made or at least suspected in the majority of instances, on clinical grounds alone.

COMMENT

A study of this type has a number of advantages. We naturally would have preferred to see all the cases ourselves. Finding it necessary in most

instances to obtain the clinical data from the patients' charts, it was not always possible to determine whether the attack was the first or second or third, and whether various physical findings were present. However, a group of cases such as these presents a cross section of the clinical picture of acute myocardial infarction as seen by the average physician and hospital staff member. The clinical features are sufficiently characteristic to arouse suspicion of the presence of an acute myocardial infarction in most instances without laboratory assistance. Laboratory procedures should be considered as merely confirmatory.

SUMMARY

1. A series of 378 cases of acute myocardial infarction is presented.
2. The incidence of males to females was 3 : 1.
3. Myocardial infarction occurred at a later period in women, the average age for women being 61.6 years, for men 56.7 years.
4. The immediate mortality roughly increased with advancing years, and was a bit greater in women.
5. Pain was reported in 90 per cent of cases, dyspnea in 76 per cent, cyanosis 46 per cent.
6. Temperature was elevated in 66 per cent of cases, and the pulse was above 100 in 47 per cent.
7. Hypertension and cardiac failure were much more frequent in the female than the male.
8. Friction rub was present in 12 per cent of the cases.
9. Fifty per cent of the patients were admitted with a diagnosis of acute myocardial infarction. On admission, 20 per cent had no diagnosis referable to the heart.

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STUDIES IN ACUTE MYOCARDIAL INFARCTION. II. LABORATORY PROCEDURES AS DIAGNOSTIC AIDS*

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IN a previous paper [1] we discussed the clinical features presented by 378 cases of acute myocardial infarction. An evaluation of the laboratory procedures commonly used in this condition was also made, based upon these 378 cases. The procedures specifically considered in this study were the leukocyte count, the sedimentation rate, the blood sugar, and the electrocardiogram.

The Leukocyte Count. Levine and Tranter [2] first pointed out the presence of leukocytosis in acute myocardial infarction. Libman [3] emphasized its value in the differential diagnosis in 1925, stating that leukocytosis occurred in almost every case and might be demonstrated as early as two hours after the acute attack. The leukocytosis obtained after an acute myocardial infarction is of relatively short duration and may persist for but a few days. This probably accounts for the varying incidence of leukocytosis reported by a number of authors. Master et al.[4] found leukocytosis in 60 per cent of their cases. Levine [5] found a white blood cell count above 10,000 per cu. mm. in 70 of 74 cases. In a recent study of 50 cases of acute myocardial infarction observed from the first day of the attack, Shilleto, Chamberlain and Levy [6] noted leukocytosis in 96 per cent of their cases.

In our series, white blood cell counts were performed on 328 patients. Of these, 244 or 74 per cent had counts above 10,000 per cu. mm. The distribution curve of these counts is seen in figure 1. The greatest number by far occurs between 8000 to 16,000. Many of these cases were seen after the optimum time for demonstration of a leukocytosis. We believe, just as Libman,[3] Levine,[5] Shilleto et al.[6] have reported, that 95 per cent or more of cases of acute myocardial infarction will exhibit a leukocytosis if the count is taken early and repeated frequently enough.

Although the question of prognosis is not specifically considered in this article, a glance at table 1 would suggest that the prognosis was more ominous, the higher the leukocyte count.

Sedimentation Rate. It is commonly accepted that a rapid sedimentation rate accompanies an acute myocardial infarction. However, few studies of this topic have been made. Rabinowitz, Shookhoff and Douglas [7] first reported this finding in 10 cases of acute myocardial infarction. They [8] later reported 29 cases, all of which showed abnormally rapid sedimentation rates at some time during their illness. Riseman and Brown [9] and Gorham

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and Thompson [10] felt the rapid sedimentation rate was one of the most constant findings in coronary thrombosis. Shilleto et al.[6] found it increased in 98 per cent of their cases.

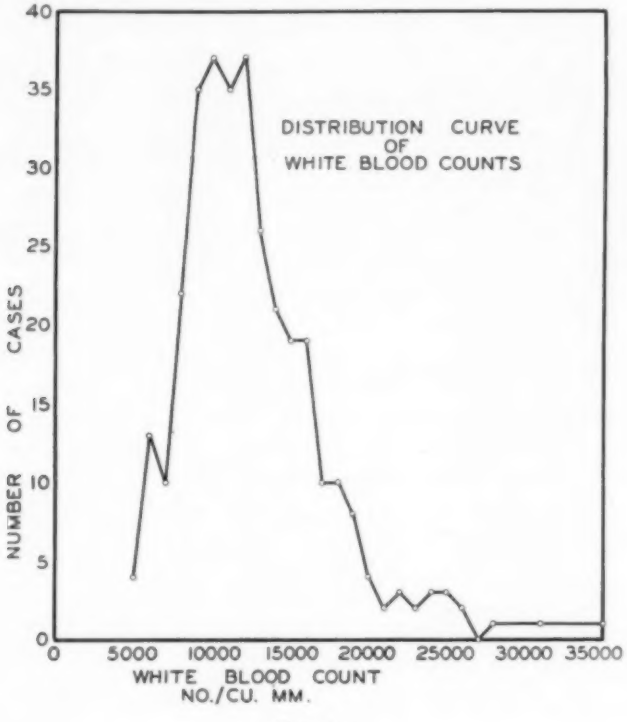

FIG. 1.

The fastest rates occur two to five days after the acute seizure, and return to normal within 13 to 39 days.[8] Emphasis has also been placed on the length of time the sedimentation rate remains rapid. It is our practice to keep the patient in bed until the sedimentation rate returns to normal. In the

TABLE I

White Blood Cell Counts

	Number of Cases	Fatalities	
		No.	Percentage
5,000– 9,900	84	18	21%
10,000–14,900	156	44	28%
15,000–19,900	66	27	41%
20,000–24,900	14	5	36%
25,000–29,900	6	4	66%
30,000–34,900	1	1	100%
35,000–39,900	1	1	100%
Total	328	100	

more extensive infarcts, sedimentation rates may remain rapid for as much as 8 to 10 weeks.

In our series of cases, sedimentation rates were obtained (by the Cutler method) [11, 12] in 180 patients. Of these, 171 or 95 per cent exhibited abnormal curves. No case was considered abnormal unless the maximum drop in at least one five minute period exceeded 1 mm.

Blood Sugar. Levine [5] first called attention to the glycosuria and hyperglycemia that may accompany an acute myocardial infarction. We did not specifically consider glycosuria here, in view of the fact that it was not always possible to evaluate the influence of hypertonic glucose previously given as a therapeutic measure.

Blood sugar determinations were done on 289 of our 378 cases. Of these 289 patients, 94 had blood sugars above 120 mg./100 c.c. Only 34 of this group had previous evidence of diabetes. The hyperglycemia that may accompany an acute myocardial infarction is more than a mere academic finding. Frequently it will be the first evidence of an unsuspected diabetes. However, patients with an acute myocardial infarction may exhibit transient non-diabetic hyperglycemia. Insulin therapy is of course contraindicated in these cases.

TABLE II

Electrocardiographic Diagnosis

	Number of Cases	Percentage
Anterior Infarction	168	52%
Posterior Infarction	109	34%
Myocardial Infarction, Location Uncertain	22	7%
Electrocardiogram Not Diagnostic	16	5%
Bundle Branch Block	6	1%
Total	321	

The Electrocardiogram. In a separate presentation we plan to consider in detail the electrocardiographic localization of the various types of myocardial infarction. This study is limited to a consideration of the value of the electrocardiogram in diagnosing an acute myocardial infarction.

One must realize the possibilities and limitations of electrocardiography. In the human being abnormal electrocardiograms have been obtained as early as 12 hours after the acute attack.[13] Some cases may not exhibit definite abnormalities for 10 to 14 days. Barnes [13] found that absence of typical electrocardiographic changes was due to: (1) failure to take sufficient tracings, (2) the presence of multiple fresh infarctions, (3) the presence of bundle branch block, (4) the presence of pericarditis, (5) a critically ill patient. If consideration is given to these factors and the electrocardiographic patterns described by Levine,[5] Wolferth and Wood and their collaborators,[14, 15, 16, 17] and Master et al.,[18] the electrocardiogram should make possible the diagnosis and location of an acute infarction of the myocardium in practically every case.

Electrocardiograms were taken in 321 of our 378 cases. The distribution of these cases is seen in table 2. It will be seen that the electrocardio-

gram revealed the presence of acute myocardial infarction in 299 or 94 per cent of our cases. Of the 22 cases in which the electrocardiogram was not diagnostic, 11 had only one tracing and six exhibited bundle branch block. One normal or indefinite electrocardiogram, therefore, does not exclude the presence of an acute myocardial infarction. If a number of tracings taken over a period of 10 to 15 days fail to exhibit progressive or regressive changes, then one seems fairly safe in eliminating the presence of an acute myocardial infarction.

Summary and Conclusion

1. A study was made of the value of various laboratory procedures in the diagnosis of 378 cases of acute myocardial infarction.

2. Of 274 patients, 74 per cent had leukocyte counts above 10,000/cu. mm. If seen at the optimum time 95 per cent or more should exhibit leukocytosis.

3. In 180 patients 95 per cent showed a rapid sedimentation rate.

4. Blood sugar determinations were made in 289 patients. Ninety-four of these patients had hyperglycemia, and only 34 had previously known diabetes.

5. The electrocardiogram was diagnostic of acute infarction in 94 per cent of 321 cases.

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THE TREATMENT OF HYPERTENSION: COMPARISON OF MORTALITY IN MEDICALLY AND SURGICALLY TREATED CASES *

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IN previous papers the results of various observations on the course of hypertension were presented.[2] The purpose in the present paper is to compare the observations on a series of medically treated patients with those of an analogous series in which treatment was by so-called specific surgery.

A series of 244 selected patients, all under 50 years of age, was included in this study because the period of observation of 5 to 10 years seemed adequate to evaluate the results and because the time period lends itself to comparative study.

Wagener and Keith [6] and Peet et al.[4] grouped their series of medically and surgically treated cases on the basis of what they believed was the one definite and objective aspect, the retinal changes. The former [6] stated: "The present series of cases offers a good control for any specific form of therapy, as treatment consisted of general measures, especially with regard to diet and rest, and the regular use of sedatives." Peet et al.[4] accepted this statement at face value.

In the tables are presented the comparative mortality statistics of Peet and his co-workers [4a] on 350 patients treated surgically and my series of 244 patients observed medically. I could not compare my series fully with the 76 cases reported in their second paper [4b] because of the classification used, based on the retinal changes.

TABLE I

Sex Distribution

Sex	Peet et al.		Flaxman	
	Number	%	Number	%
Males	165	47	190	78
Females	185	53	54	22

The classification of essential hypertension on this aspect alone may lead to a distorted perspective of a highly complex subject. Any attempt to classify hypertension solely on the basis of a single criterion, such as the height of the blood pressure,[3a] the size of the heart, the electrocardiographic abnormalities, or the urinary findings alone,[3b] is considered unreliable. Woods and Peet [4b] qualified their findings rather cautiously by the statement:

* Received for publication August 28, 1942.

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"It still remains to be seen whether or not the present interpretation and classification of fundus changes offer a true means of prognosis in hypertension."

To obviate any disputed factors I have selected these patients on the basis of the criteria by which they [4b] chose their cases for operation. Briefly, the criteria were:

Age: perferably under 50 years.
Renal function: non-protein nitrogen of the blood under 45 mg. per 100 c.c., and urine concentration above 1.012.
Cardiac status: a compensated heart.

TABLE II
Age Distribution

Age Groups	Peet et al.		Flaxman	
	Number	%	Number	%
Under 29	24	8.3	4	1.7
30 to 39	90	31.0	63	26.0
40 to 49	174	60.7	177	72.3

TABLE III
Distribution of the Blood Pressure Levels

Pressure in Mm. Mercury	Peet et al.		Flaxman	
	Number	%	Number	%
Systolic				
270 plus	7	2	12	5
240 to 269	69	20	46	19
210 to 239	150	43	99	41
180 to 209	109	31	75	30
140 to 179	15	4	12	5
Diastolic				
155 plus	42	12	27	11
140 to 154	86	25	49	21
125 to 139	106	30	88	36
110 to 124	95	27	69	28
95 to 109	21	6	11	4

There is a difference of opinion as to the relation of sex to the course and severity of hypertension. It is thought by the majority that males tolerate hypertension less well than females. The disproportion of the sexes in the two series would seem to be of considerable importance in the ultimate mortality. However, Woods and Peet [4b] took the view that a revision of this idea is necessary and compared their series of surgically treated cases with the Wagener-Keith [6] series of medically treated cases on that basis. Therefore, I have taken the same course in this comparison (table 1).

The patients under 50 in the Peet series of 350 cases were compared with the 244 in this study. Those in the former were somewhat younger, 39.3 per cent under 40, as compared with 27.7 per cent under that age in my series (table 2).

A comparison of the blood pressure levels of the two groups (table 3) reveals a close similarity. In both groups 65 per cent had systolic pressures above 210 mm. of mercury; 67 per cent of the Peet [4a] series had diastolic pressures above 125 mm., and in my study 68 per cent had readings above this level.

Table 4 indicates the comparative mortality in the two groups of cases.

TABLE IV
Mortality Rates

	Cases	Deaths	Mortality %
Peet et al.	350	107	30.5
Flaxman	244	77	31.0

TABLE V
Causes of Death

Causes	Peet et al.		Flaxman	
	Number	%	Number	%
Congestive heart failure	29	27.5	42	54
Cerebral hemorrhage*	31	29.5	5	6
Uremia*	17	16.0	19	27
No data	13	12.5	—	—
Operative	12	11.0	—	—
Others	5	4.5	2	2
Coronary thrombosis*	—	—	9	11

* Uncontrollable factors.

A study of the causes of death (table 5) reveals some interesting comparisons. The causes of death may be divided into the controllable factors (congestive heart failure and operations) and the uncontrollable factors (cerebral hemorrhage, uremia, and coronary thrombosis). It is the unpredictable factors which make hypertension such a dreaded sign. In the Peet series [4a] 45.5 per cent of the deaths were due to causes beyond control, and in the present study 44 per cent of the deaths were in this class.

Weiss [7] commented on the high percentage of malignant hypertension reported, 67 per cent in the Wagener-Keith series [6] and 32 per cent in the second Peet report.[4b] This is a very unsettled subject, not only from the medical point of view, but also from the surgical standpoint.[1] To this comment Peet and Woods [5] replied that "we do not see 'the kinds of patients who comprise most of the cases seen in private practice' but instead are asked to treat the patients who have not gained relief after a thorough trial of

medical treatment." In subjecting such patients to operation a good deal may have been taken for granted, as the question of "a thorough trial of medical treatment" leaves much to be desired.

In the present series, of the 244 patients under 50, the diagnosis of malignant hypertension was made in 32 (13.1 per cent). In 26 of the 32 cases the diagnosis was substantiated at autopsy. Nine (34 per cent) of the 26 confirmed cases were alive at the end of five years. In the Peet series of 76 cases,[4b] in which 24 (32 per cent) were clinically diagnosed as malignant hypertension, eight (33 per cent) of the 24 were alive at the end of five years. Such a close similarity between the mortality rates of the two groups suggests that the so-called specific surgery has little if any effect on the course of malignant hypertension. It has been conceded that the available medical therapy has no effect on the rapid course that leads to an early fatal termination in two-thirds of the cases of malignant hypertension.

Comment

Various aspects of the disease have not been considered in detail in this study. These include the subjective symptomatology, the degree of incapacitation, the cardiac status (based on the electrocardiogram and the teleroentgenogram), and the blood pressure changes. All are factors that depend on personal observation and interpretation.

The personal attitude toward high blood pressure should not be discarded lightly. Some take high blood pressure as an everyday fact, whereas others become greatly alarmed and agitated over the finding of this sign. The former type of patient generally has few, if any, of the numerous psychoneurotic symptoms which the latter may have, in profusion, such as headache, nervousness, irritability, fatigue, dizziness, and many more. The psychic factor is of the utmost importance as it profoundly affects a patient's attitude toward his blood pressure. I have shown that it is entirely possible for hypertensive patients to have a distinct apathy on the subject, which may aid them greatly in living longer.[2b]

Closely related to the symptomatology is the question of incapacitation. Inability to work, from the patient's point of view, does not establish incapacitation. Desire to work, based on the patient's reaction to his high blood pressure, does answer this question.[2e]

Interpretation of the cardiac status in hypertensive patients who have not suffered congestive heart failure requires the most careful consideration. None of the abnormal findings, such as the degree of axis deviation or the T-wave changes in the electrocardiogram and the degree of cardiac enlargement, are inflexible factors. The changes may be slight, moderate, marked, or very marked (graded as 1, 2, 3, and 4, respectively, by some), but these are still indecisive variables and should not be used either to estimate the degree of involvement or the prognosis.

Among all the factors mentioned, the blood pressure changes are the most labile. Peet et al.[4a] stated that of the patients they studied 51.4 per cent with adequate postoperative data had a significant reduction in blood pressure, and approximately half of these patients had pressures reduced to normal or markedly reduced. In the medical treatment of essential hypertension my observations reveal that the elevated blood pressure gradually decreases until it is approximately normal or markedly reduced in one-third of all hypertensive subjects.[3a]

Summary

A study of the mortality in patients with essential hypertension medically observed as compared with that of a series of surgically treated cases revealed little difference between the two groups. It is doubtful whether so-called specific surgery alters the course and prognosis in cases of hypertension, including those with malignant hypertension.

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CASE REPORTS

AURICULAR FLUTTER WITH AURICULOVENTRICULAR HEART BLOCK *

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Experimental auricular flutter was first produced in dogs by MacWilliam,[1] in 1887. Since the introduction of the string galvanometer this abnormality has been recognized frequently in man. The finding of complete heart block is not unusual. However, the combination of auriculoventricular block with auricular flutter is a rare and unique association of abnormalities. The occurrence of such a combination warrants the following case presentation.

Case Report

A 60 year old white man came under observation in August 1940, with the following history. While waiting for a trolley car he lost consciousness and fell to the ground striking the right parietal region of his skull against the pavement. An ambulance was summoned and he was transported to the hospital in syncope. A diagnosis of heart block with Stokes-Adams syndrome was made. The pulse rate was 16 per minute. Repeated injections of adrenalin chloride solution 1–1000 were given. The patient regained consciousness after several hours and was removed to his home. Examination revealed a well developed man who was drowsy but could be roused by loud speech and by stimulation. He was disoriented as to his location, the time of the day and the events of the early morning. Speech was thick and sensorium was clouded. Questions were answered poorly. Blood pressure was 160 mm. Hg systolic and 70 mm. diastolic; pulse rate, 36; height, 68 inches; and weight, 190 pounds. There was a hematoma in the right parietal region of the skull extending from about an inch above the lobe of the ear to the tip of the mastoid bone. Both pupils reacted to light. The drums were thickened. Arcus myringis was present bilaterally. The lips were cyanotic. There were moist râles at the bases of both lungs posteriorly. The maximum precordial impulse could neither be seen nor felt. The heart was enlarged by percussion, both to the right and left. The aorta was wide. The heart tones were of fair muscular quality. A short soft systolic murmur was audible at the apex and was transmitted to the axilla. There was also a harsh systolic murmur with its maximum intensity in the fourth intercostal space audible to the right of the sternum. There was a marked bradycardia. Observation of the pulsations visible in the neck revealed that they occurred at a rate five or six times as frequent as were systolic contractions heard at the apex. There was slight pitting edema of both lower extremities. The Babinski reflexes were positive bilaterally.

The past history revealed the following: About 18 months prior to the time the patient came under observation, while working near an unguarded pit in a laundry, he fell, striking his left shoulder and left anterior chest against the boiler in the pit and against the concrete walls of the pit. Since that time he had been unable to work because of shortness of breath and pains in his chest, back and left shoulder. Al-

* Received for publication May 1, 1942.

though he could not perform his regular work, he would walk about the house and at times even felt well enough to leave his home to visit his physician's office for treatment. During this interval his wife noted that on several occasions he became drowsy and remained so for one half to three quarters of an hour. He came out of these drowsy spells suddenly and would remain alert. At intervals during the next year and a half, electrocardiographic records were obtained. They showed a persistent heart block with an impure flutter which at times looked like auricular fibrillation.

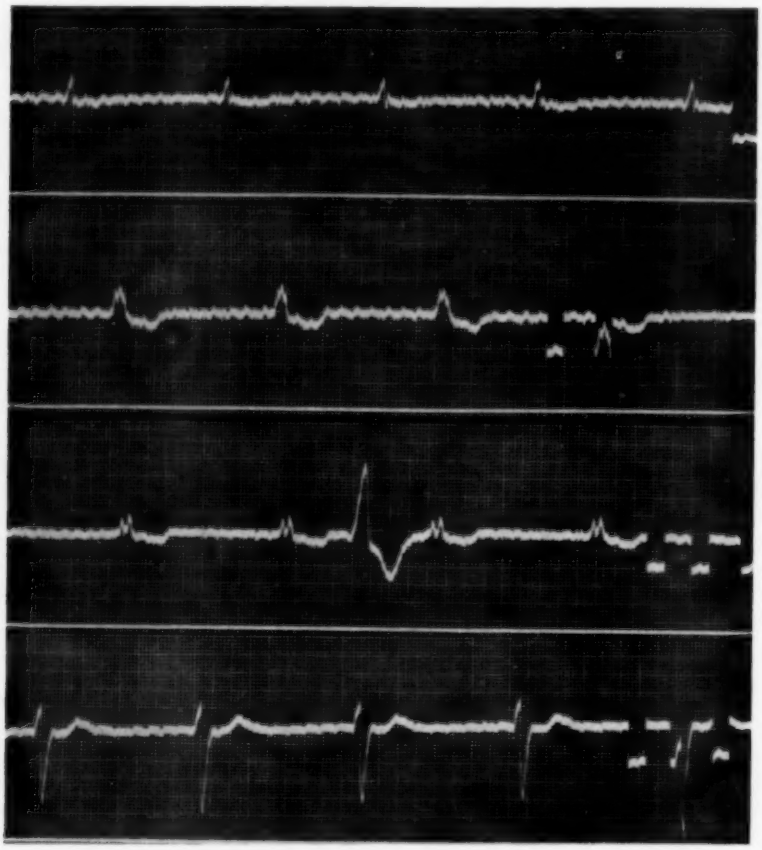

FIG. 1. Impure flutter, bundle branch block, severe myocardial damage, occasional premature ventricular extra contraction.

The ventricular rhythm was regular during this entire time. Laboratory data obtained two months after the accident revealed the following: hemoglobin 81 per cent; red blood cells 4,680,000; sedimentation rate 11 mm. in 1 hr.; Wassermann reaction negative. Urine: Specific gravity 1.016; albumin, faint trace; no cellular elements present in the centrifuged specimen. Blood chemistry: Sugar 92 mg. per cent; uric acid 2.2 mg. per cent; creatinine 1.3 mg. per cent; urea 16.3 mg. per cent; cholesterol 223 mg. per cent; total protein 6.2 mg. per cent; albumin 2.8 mg. per cent; globulin 3.3 mg. per cent; albumin globulin ratio 0.8; non-protein nitrogen 30.6 mg. per cent. Basal metabolic rate minus 20 per cent.

Electrocardiogram (figure 1) revealed an impure flutter, bundle branch block and severe myocardial damage. There were occasional premature ventricular extra contractions. A conventional teleroentgenogram (figure 2) revealed the heart to be considerably enlarged in all diameters, especially in the transverse diameter. The aortic knob was tortuous and pronounced. There was accentuation of the broncho-vascular markings. Teleroentgenogram dimensions were: Aorta 7 cm.; right transverse 10.5 cm.; left transverse 11.5 cm.; intrathoracic 30.0 cm. The heart occupied approximately 70 per cent of the intrathoracic diameter, indicating considerable hypertrophy.

The remainder of the past history was non-contributory, beyond the fact that the patient had been an engineer for 30 years and had no previously recorded illnesses.

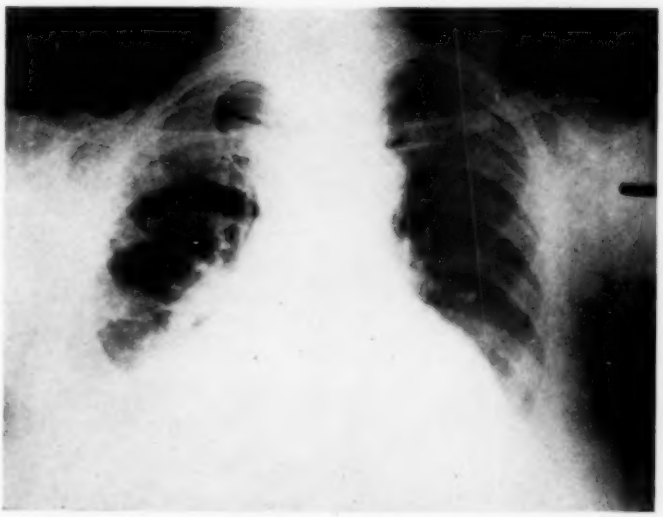

FIG. 2. Conventional teleroentgenogram showing marked cardiac hypertrophy.

Progress. On the second day after the episode of August 1940, the patient developed a coarse tremor of both upper extremities which was exaggerated at times so as to assume almost convulsive proportions. These tremors lasted for two or three minutes at a time and then subsided. His speech improved but his conversation was still incoherent. An electrocardiogram (figure 3) revealed auricular fibrillation with impure flutter, left bundle branch block and pulsus alternans. On the fourth day the patient's sensorium began to clear so that he responded to questions intelligently. His apical pulse was 50 per minute.

On the fifth day he developed a chill with an elevation of temperature to 102° F. The respirations were rapid. Physical examination revealed evidence of pneumonic consolidation at the base of the left lung. The laboratory data were as follows: Hemoglobin 82 per cent; red blood cells 4,600,000; white blood cells 13,000, with a differential of polymorphonuclear neutrophiles 74 per cent; lymphocytes 23 per cent; eosinophiles 2 per cent; monocytes 1 per cent. The sedimentation rate was 26 mm. in 1 hr. Westergren method. Blood sugar was 112 mg. per cent in serum; urea 30 mg. per cent in serum. The urine contained 4 plus albumin. On microscopic study, hyaline and granular casts were easily identified. For the next few days the patient alternated between periods of clouded sensorium and mental alertness. At times he became restless. The periods during which he was mentally clear increased

and his condition improved sufficiently so that on the fourteenth day the patient was able to get out of bed.

An electrocardiogram (figure 4) taken on the sixteenth day revealed auricular flutter and left bundle branch block. The auricular rate was 375 and the ventricular rate was 37. The white blood cell count had returned to normal. The differential count was also normal. The temperature had declined. The respirations though irregular were 18 per minute.

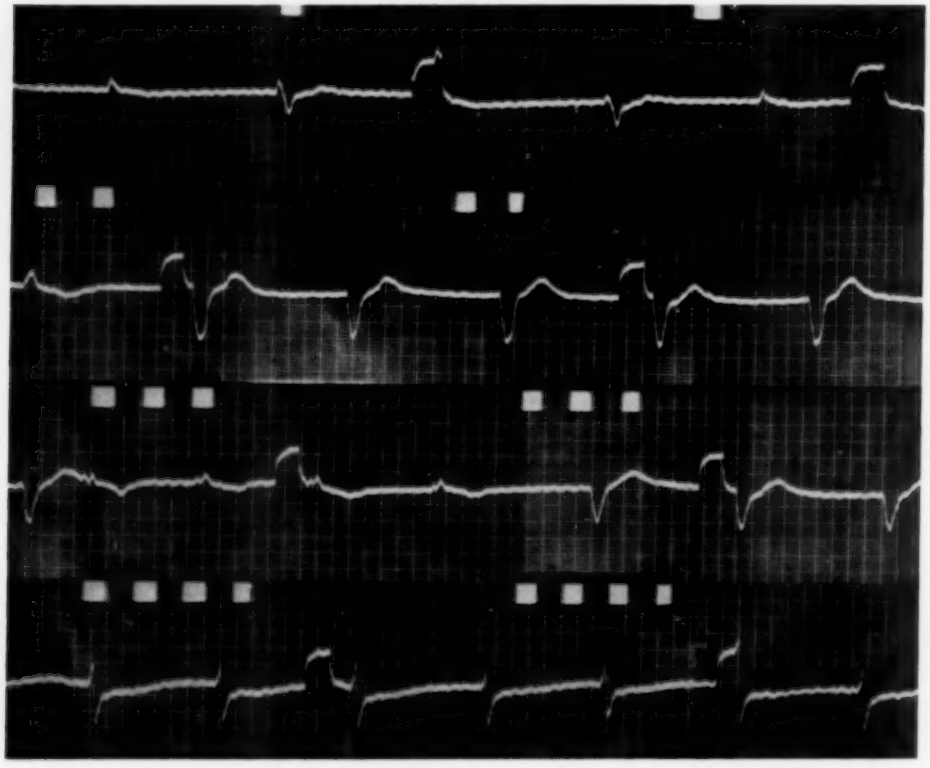

FIG. 3. Auricular fibrillation, impure flutter, left bundle branch block, pulsus alternans.

On the thirtieth day the patient developed a severe and extensive herpes zoster involving the segmental distribution of the right tenth thoracic nerve. During this time he complained of shortness of breath and discomfort in the recumbent position. Thiamine chloride in large doses was given daily. During the next seven days the herpetic lesion subsided but the pain remained though it was not quite so severe.

On the forty-second day the patient became irrational, excited and violent. Large doses of hypnotics were required to keep him under control. He refused all nourishment so that parenteral feeding became necessary.

On the forty-fifth day the patient presented evidences of pneumonic consolidation at both bases. Respirations were rapid. The temperature was 102° F. He developed evidences of nitrogen retention and had irregularly recurring convulsive movements of the muscles of the face and right hand. Laboratory data revealed the following: white blood cells 22,000, with 78 per cent polymorphonuclears. Sedimentation rate 22 mm. in 1 hr. Urea nitrogen 48 mg. per cent; creatinine 1.8 mg.

FIG. 4. Auricular flutter, left bundle branch block. Auricular rate 375—Ventricular rate 37.

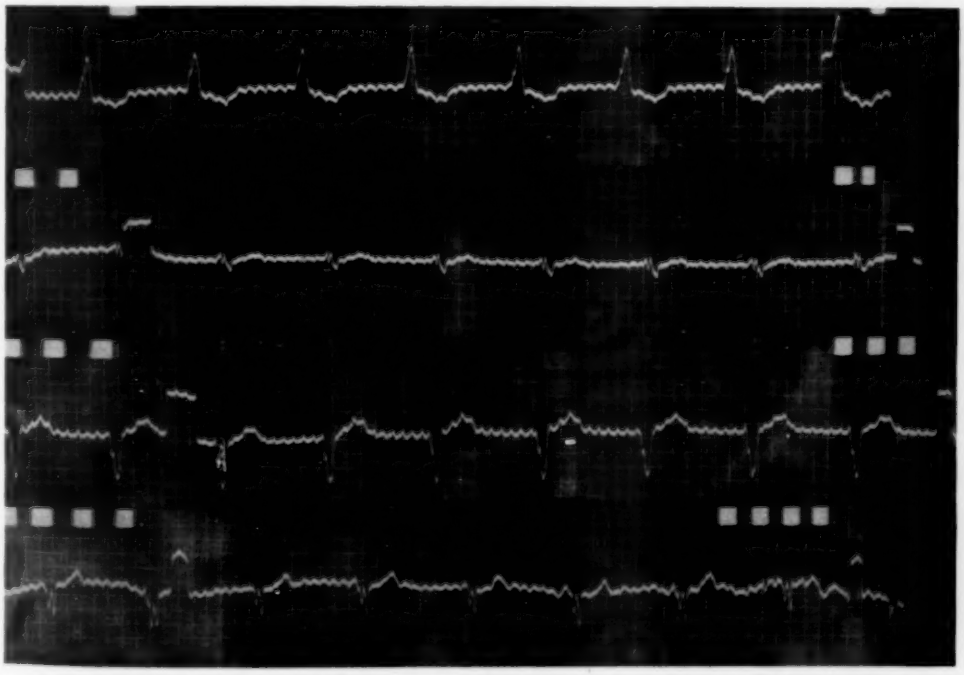

FIG. 5. Auricular flutter, auriculoventricular heart block. Auricular rate 375—Ventricular rate 40.

per cent. The patient's condition became progressively worse. An electrocardiogram (figure 5) taken on the forty-seventh day revealed auricular flutter and auriculoventricular heart block (auricular rate 375, ventricular rate 40). On the following day he lapsed into coma and on the forty-ninth day following the onset of his last illness he died.

The pertinent findings at necropsy* were as follows: The lungs were nonadherent. There was no free fluid in the pleural cavities. The left lower lobe and the middle right lower lobes were the seat of bronchopneumonia. The heart weighed 950 grams. It appeared to be twice the normal size, with left ventricular enlargement. Section of the left ventricle revealed the muscle to be three quarters of an inch in thickness and yellowish brown in color. There was advanced myofibrosis in the interventricular septal portion of the lateral wall, as well as in the wall of the ventricle itself. The pectinate muscles were well developed. The mitral valve admitted four fingers. There was no thickening of the free border of the valve, which appeared to be competent. The remaining valves were competent. There was advanced atherosclerosis of the aorta. The coronary arteries were patent. The liver extended beyond the free border of the ribs for a distance of about one inch; it cut with gritty resistance and appeared to be somewhat edematous. The architecture was not easily discernible. There were marked congestion and evidence of fatty change. The pancreas showed fibrosis. The adrenals were normal in appearance. The kidney capsule stripped with difficulty, leaving granular, irregular surfaces. On section there were marked congestion, a granular appearance of the cut surface, and an increased amount of pelvic fat. The cortex and medulla were pallid and were not sharply demarcated. The vessels were sclerotic. There were occasional cortical and medullary cysts. The ureters and bladder were normal. The prostate was somewhat enlarged. The spleen was slightly increased in size and rather firm. On cut section it was markedly congested. The Malpighian bodies were not easily discernible. The gastrointestinal tract was grossly negative. Section of the scalp and removal of the calvarium revealed marked congestion and edema of the brain. Section of the brain revealed no evidence of tumefaction, hemorrhage or softening. The basilar vessels were markedly sclerotic. Anatomic diagnosis: Bronchopneumonia; myofibrosis cordis; chronic interstitial nephritis.

Discussion

The term total heart block is generally employed to designate an abnormality caused by a partial or complete interference with the conduction of impulses from the auricles to the ventricles. This interference may manifest itself merely as a pause which may be somewhat longer than usual between the contractions of the auricles and ventricles or as an occasional irregular or total failure of the ventricles to respond to the auricular contractions. In view of the fact that the bundle of His constitutes the only functional connection between the auricles and ventricles a disturbance in this conduction pathway can result only from damage to the cardiac musculature through which this tissue courses. Such abnormalities may result from cutting, crushing or in some other way injuring that region of the auriculoventricular junctional tissue which houses the fibers of the bundle of His. Probably all cases have some disorder in this muscular tissue, though the exact nature of the lesion is often a matter of conjecture.

Auricular flutter may result from acute or chronic degeneration of the auricular musculature or as a result of an acute toxemia. Cohn [2] has suggested

*The autopsy was performed by Dr. R. W. Auerbach, Medical Examiner, City of New York. The authors wish to thank Dr. Auerbach, for a report of his findings.

that flutter may be due either to the failure on the part of the sinoauricular node to respond to stimulation coming through the vagus or to failure of the impulse coming through the vagus to reach the sino-auricular node. Lewis and his co-workers [3] have demonstrated experimentally that the circus movement which underlies auricular flutter is provoked when the effective shock enters the auricular musculature while the latter is in a critical condition. This critical condition is a state of partial refractoriness brought about by a high rate of auricular activity. Wilson [4] observed auricular flutter following vagus stimulation and attributed the increase in the circus rhythm either to shortening of the path of a circus wave, a reduction in the length of the refractory period of the auricular musculature, or to a shortening of the absolute refractory period thus permitting the circus wave to accept a shorter path. Although there still remain some adherents to the theory that auricular flutter is brought about by a succession of auricular systoles which are initiated at such a rapid rate that the ventricles can no longer keep up with the accelerated auricular rate, the majority of opinions [5] at the present time favor the circus movement theory.

The first case of auricular flutter associated with complete auriculoventricular block was reported by Jolly and Ritchie [6] in 1910. Their patient was a 61 year old man whose auricular rate, as recorded on the string galvanometer, was 273 per minute while the recorded ventricular rate was 35 per minute. Since then case reports have been added to the steadily growing literature recording the association of this unique pair of abnormalities. Willius [7] noted that auricular flutter with complete heart block occurred but once in 158 cases of auricular flutter studies at the Mayo Clinic. Crawford and DiGregorio [8] noted this unusual association but twice in the study of 20,000 consecutive electrocardiographic records at the Kings County Hospital. The rarity of these abnormalities is shown by the fact that a critical review of the literature in 1937, by Jourdonais and Mosenthal,[9] yielded only 29 acceptable cases, including their own. Crawford and DiGregorio added two cases which came under their observation, thus bringing the total number of cases of auricular flutter with auriculoventricular heart block to 31. Of this entire series only four occurred in women. The age distribution ranged from 13 to 74 years, with 80 per cent occurring in individuals beyond the fifth decade of life. Auricular flutter with complete heart block has been reported as occurring in congenital, thyrotoxic, rheumatic and syphilitic heart disease. The greatest incidence has been noted in patients suffering with arteriosclerotic heart disease. In the patient whom we had under observation for a period of 18 months, there was underlying arteriosclerotic heart disease.

Summary

A report is presented of a case of auricular flutter with complete heart block in a male adult 60 years of age with underlying arteriosclerotic heart disease.

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THECOMA OF THE OVARY ASSOCIATED WITH PLEURAL EFFUSION AND ASCITES; MEIGS SYNDROME *

By Martin Perlmutter, M.D., *Brooklyn, New York*

In 1937, Meigs and Cass [1] reported seven cases in which a benign fibroma of the ovary was accompanied by a serous transudate in the peritoneal cavity and in one or both pleural cavities. In all cases the surgical removal of the benign pelvic tumor proved to be the only step necessary to relieve the patient of the ascites and pleural effusion. These investigators pointed out that "the importance of such lesions in medical and surgical problems seems very great, for unexplained pleurisy with effusion and unexplained ascites are problems that occasionally confront our internists. They must be made aware of the possibility of a simple tumor being responsible for such a condition." Despite this, the only articles written about this syndrome since 1938 have appeared in the surgical literature. The case described below is unique in that the tumor was a thecoma of the ovary and not the usual fibroma of the ovary.

Meigs,[2] in 1939, in an excellent review of the 15 recorded cases, clearly outlined the clinical and pathological features of the syndrome, which now bears his name. Since then five additional cases have been reported by Bomze and Kirshbaum,[3] Harris and Meyer,[4] Lock and Collins,[5] and Glass and Goldsmith.[6] In all of these reports the pelvic tumor was an ovarian fibroma.

Salmon,[7] in 1934, reported a similar syndrome of ascites and hydrothorax in two patients with benign uterine fibromata. Dannreuther,[8] in 1937, stated that he had observed this syndrome associated with a benign ovarian cyst, but subsequently this patient died of generalized abdominal metastases from this tumor. In 1940, Traut and Marchetti,[9] in their review of 61 cases of thecoma and granulosa cell tumors of the ovary, mentioned that in one instance hydrothorax was a prominent feature, and abdominal fluid was found at the time of the operation. The tumor in the ovary proved to be benign. Vogt,[10] in the same

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year, reported a case of granulosa cell tumor associated with hemoperitoneum and hemothorax. On the fifteenth day after this ovarian tumor had been removed, the signs of pleural effusion and ascites had disappeared. McFee, in 1941, presented a case of the Meigs syndrome associated with a multilocular cystadenoma of the ovary. Thus Meigs' prediction of 1939 that "it is possible that there are benign tumors in the pelvis other than ovarian fibroma which may be accompanied by ascites and hydrothorax" seems to have been borne out.

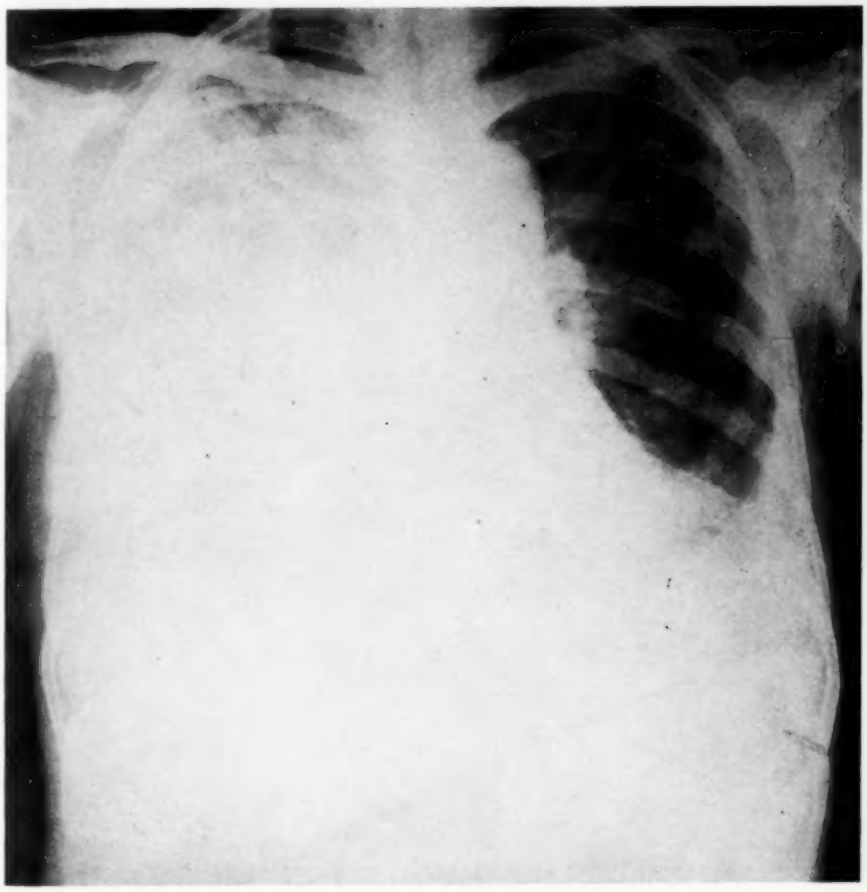

FIG. 1. Roentgenogram of chest one month preoperatively.

CASE REPORT

Mrs. E. K., a 60 year old Austrian housewife, was first admitted to the medical service of the Long Island College Division of the Kings County Hospital on October 29, 1941, complaining of shortness of breath of two years' duration, and pain in the right side of the chest for one month.

Twenty years previously a uterine fibroid tumor had been removed. Seventeen years later, a large, firm, lower abdominal mass appeared and had slowly become larger without any associated pain or discomfort to the patient. The abdominal girth had gradually increased in the past two years. The menstrual flow had been

normal until two years prior to hospitalization, at which time the menses ceased. In the preceding six months, irregular vaginal spotting and an occasional profuse flow appeared. During the previous two years dyspnea had gradually increased. At the onset of this complaint a diagnosis of pleurisy with effusion was made and corroborated by thoracentesis. Eight thoracenteses had been performed before hospitalization, the last being done eight months before admission. A dry, non-productive cough and an increase in dyspnea were noted two months after the last thoracentesis.

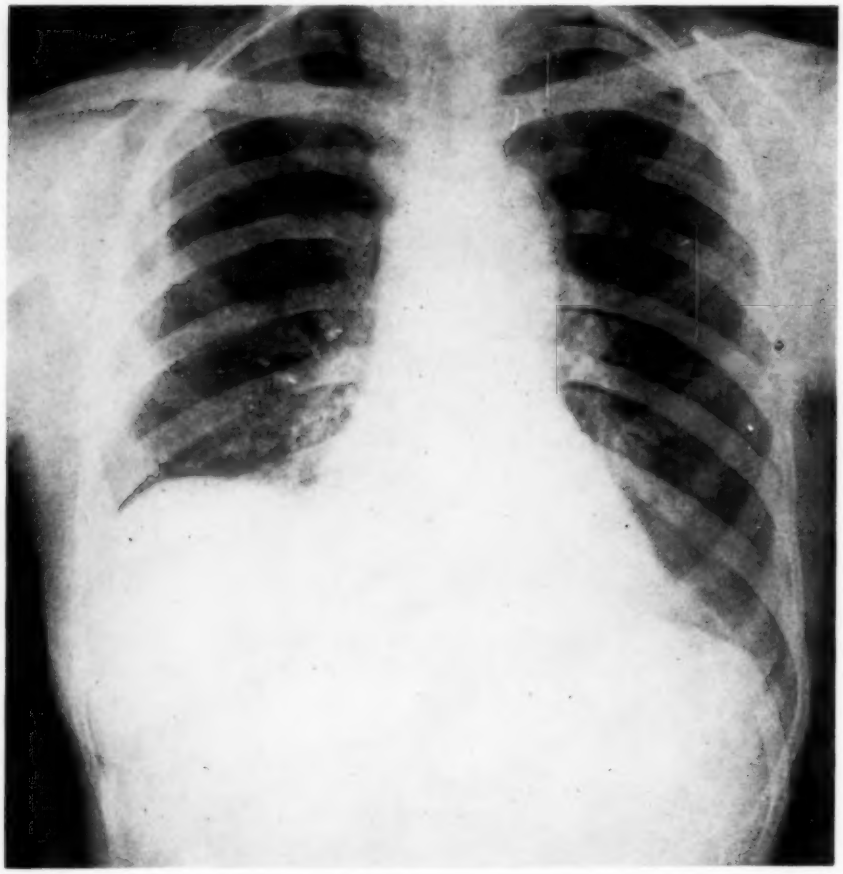

FIG. 2. Roentgenogram of chest two months postoperatively.

Right pleural pain had appeared during the preceding month. There had been a loss of 35 pounds in two years despite usual food intake. There was no history of hemoptysis, chills, fever, or ankle edema. The patient had never had rheumatic heart disease or hypertension, and there was no known contact with tuberculosis. There had been no acute respiratory disease before the onset of the present illness.

The patient had had two pregnancies, one terminating in a four months' miscarriage, and the other in a full term child.

Physical examination revealed a cachectic, orthopneic, cyanotic, elderly white woman with distended neck veins. There was no tracheal shift. No cervical nodes were palpated. The pulse rate was 65 beats per minute and the blood pressure was

120 mm. Hg systolic and 80 mm. diastolic. Classical signs of a massive right hydrothorax were noted. No abnormal signs were elicited on the left side of the chest. The heart appeared to be displaced to the left anterior axillary line but was otherwise normal. The abdomen was distended to the size of a five months' pregnancy. Shifting dullness was present. A firm, nodular, freely movable mass extended from the pelvis to two fingers'-breadth below the umbilicus. A midline operative scar extended from the umbilicus to the pubis. Vaginal examination revealed a parous introitus with a relaxed pelvic floor and senile vaginal changes. The cervix was bilaterally lacerated, mobile, and insensitive. The uterus was not felt. The mass noted on abdominal palpation appeared to arise from the pelvis. Neither adnexa was felt. The

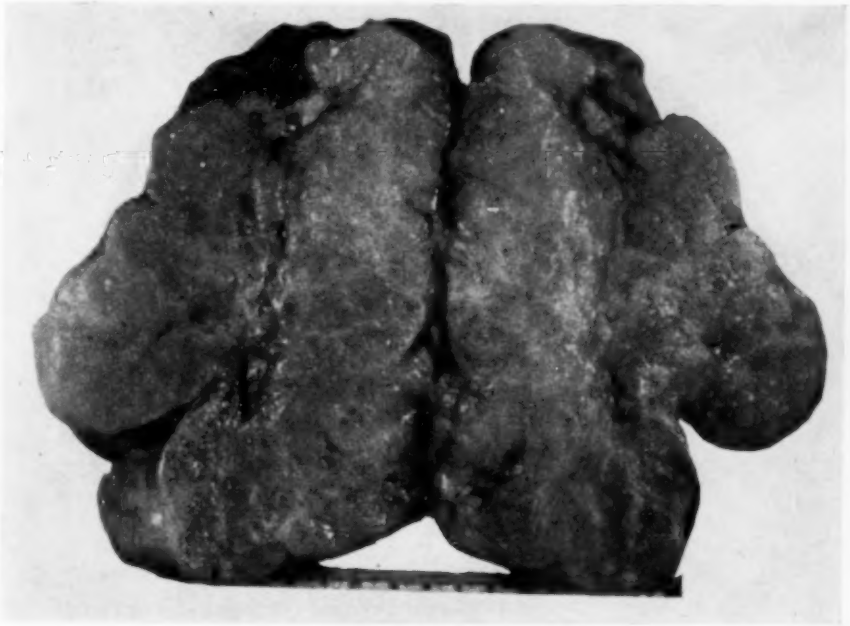

FIG. 3. Gross section of the thecoma of the ovary.

parametria and cul-de-sac were free from masses. There was blood tinged vaginal discharge. No significant adenopathy was noted.

Because of the obvious respiratory distress, a right thoracentesis was performed. Two liters of straw colored fluid were removed and another one and one half liters were removed within 12 hours. Yet within two days the dyspnea returned, necessitating the removal of another two liters of fluid. Anaerobic and aerobic cultures of this effusion were sterile. Repeated search revealed no acid fast bacilli. A few lymphocytes but no neoplastic cells were noted on stained smears of the sediment.

The pulse rate varied between 60 and 70 beats per minute. The temperature slowly rose from 98° F. to 100.2° F.

Urinalysis revealed a normal urine with a specific gravity of 1.022. Admission blood count showed 4,000,000 red blood cells and hemoglobin 10 grams. The blood Wassermann reaction was negative. Roentgenological study of the chest revealed massive right pleural effusion with a small effusion on the left side. The underlying lung parenchyma was obscured. No evidence of any metastasis was seen in the visible parts of the lung.

The patient was urged to undergo a laparotomy because the diagnosis of Meigs syndrome was considered, but she refused and signed her release from the hospital, her condition only slightly improved.

On November 14, 1941, ten days later, the patient was readmitted because of severe dyspnea. The only change in the physical findings was a palpable liver edge two to three centimeters below the right costal margin. Despite morphine and oxygen, the respirations rapidly became more labored. An emergency thoracentesis of one and one half liters, followed by the removal of another liter in 12 hours, alleviated the respiratory distress. The fluid was similar in every respect to the fluid removed during the previous hospitalization.

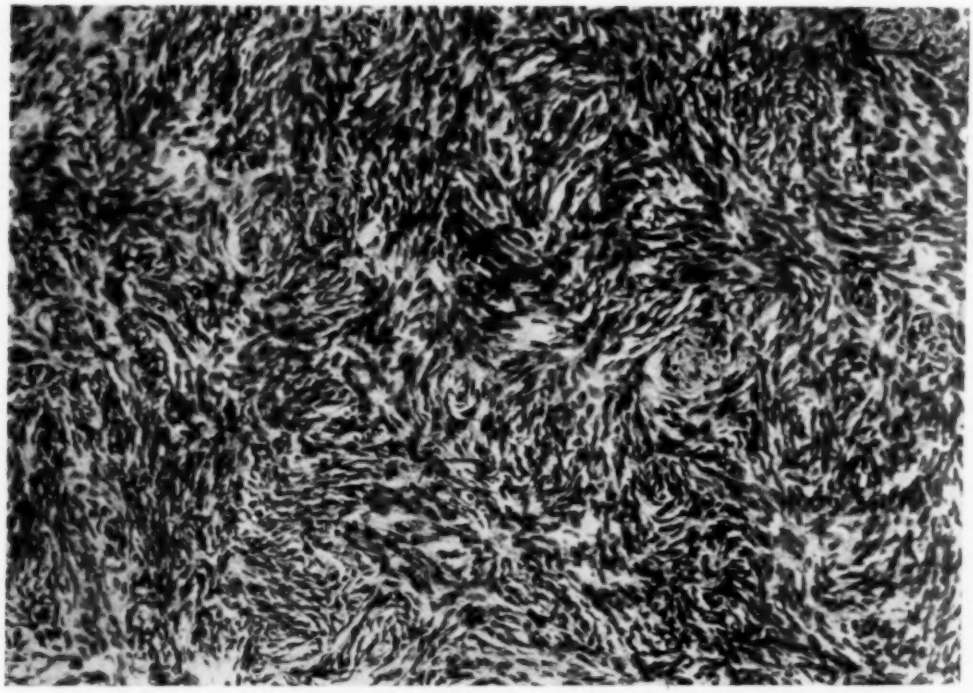

FIG. 4. Microscopic section of the thecoma of the ovary.

The patient consented to having a laparotomy performed. However, on November 22, 1941, the anesthetist considered her "a poor anesthetic risk" and advised that "only emergency surgery should be considered." Dr. Charles A. Gordon, director of the gynecological service, agreed that the patient was an extremely poor risk. However, since there was no improvement on conservative therapy, he stated that further delay was not advisable and suggested immediate operation.

On November 24, 1941, a laparotomy was performed. The patient was given morphine and scopolamine as sedatives. Local novocaine anesthesia was used. Two and one half liters of straw colored fluid were aspirated from the peritoneal cavity. The tumor arising from the right ovary was nodular and mobile. A few adhesions to the intestines were noted. The tumor and right tube were removed. The left ovary had been removed at a previous operation. The uterus, which was small and mobile, was not attached to the tumor. The liver extended seven centimeters below the right costal margin. A small fibroma, one centimeter in diameter, was seen just

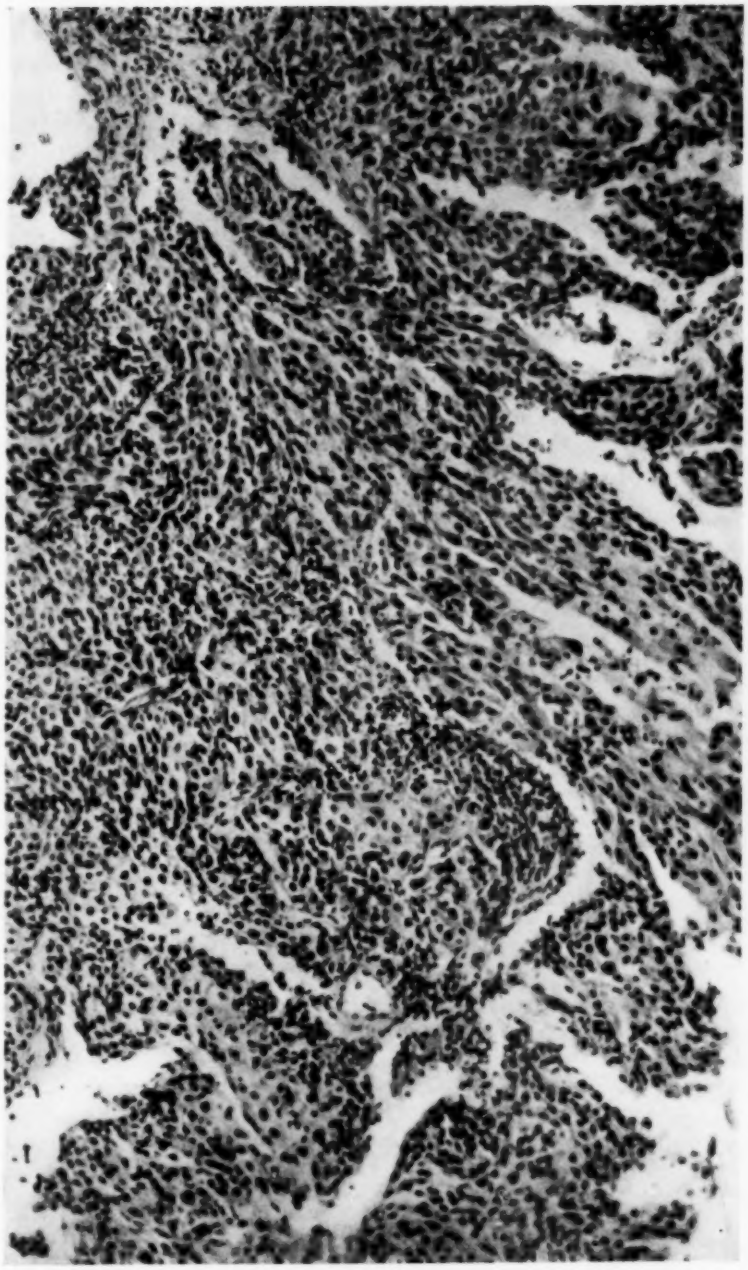

FIG. 5. Microscopic section of the carcinoma of the cervix.

above the apex of the gall-bladder. No metastatic implants were noted in the peritoneum.

The postoperative course was uneventful. On the tenth postoperative day, a slight decrease in the pleural effusion was noted. At this time the venous pressure

was 150 mm. of saline with the arm at the level of the auricle. The arm-tongue circulation time, as measured with decholin, was 12 seconds. Both of these were within normal limits. The serum protein was 5.6 grams, and the albumin-globulin ratio was 1.

Seventeen days postoperatively the signs of fluid in the right chest had disappeared almost completely. The general condition had improved remarkably, and the patient was able to walk without aid. Roentgenological study of the chest, on the twenty-first day postoperatively, revealed a marked diminution of the right pleural effusion, only a small amount remaining in the right costophrenic sulcus. The left pleural effusion had completely disappeared. On this day the patient was discharged from the hospital markedly improved.

Two months after the operation the patient had no dyspnea or orthopnea, and was able to do her house work without any discomfort. Roentgenological study revealed complete disappearance of the right pleural effusion.

The tumor measured 17 by 14 by 11 centimeters and weighed 1300 grams. It was firm, irregular, and whitish-yellow. The cut surface was firm in consistency and consisted of broad, white, fibrous streaks with semisolid triangular-shaped golden areas.

Microscopic examination revealed that the capsule of the ovary was thickened and composed of fibrous tissue. The parenchyma of the tumor consisted of whorls or bundles of large, broad, oval-shaped cells containing ample pink cytoplasm and a large, solid, light blue oval or round central nucleus. These cells were surrounded by interlacing bands of fibrous tissue. Many large plaques and sheets of hyalinized tissue were present. Intimately enmeshed in the tissue were small and large areas of vacuolated cells with flat nuclei. With Sudan III these vacuoles stained orange red. The tumor was diagnosed as a thecoma of the ovary.

Addendum. Three months postoperatively, a complete pelvic examination was performed and no abnormalities were noted.

Two months later, or five months after the thecoma had been removed, the patient was referred back to the gynecological clinic because of low back pain and mild intermittent vaginal bleeding of about six weeks' duration. At this examination, the cervix was noted to be hard, enlarged and friable. The right vaginal wall and parametrium were infiltrated by a firm tissue. Biopsy of this cervical tumor revealed a lawless proliferation of epidermoid cells which contained several mitotic figures and an occasional attempt at pearl formation. The pathological diagnosis of epidermoid carcinoma of the cervix, grades II and III, confirmed the clinical impression.

Physical examination of the patient's chest and abdomen, at this time, revealed no abnormalities. Roentgen study of the chest demonstrated complete resolution of the pleural effusion. The diaphragm was at the normal level. No metastatic areas were noted in either lung field. The bones of the lumbar spine and pelvis did not reveal any metastatic abnormality.

The patient was given roentgen therapy in preparation for radium therapy. One month after the discovery of the cervical neoplasm, she was still doing her full housework and had had no return of dyspnea or weakness.

Comment

It is of the utmost importance that every case of unexplained hydrothorax and ascites in the female be carefully investigated for the presence of a pelvic tumor. As has been stressed by Meigs, the primary pelvic tumor may, at times, be overlooked even on careful examination and abdominal paracentesis may be necessary before the pelvic mass can be felt. If this syndrome is not borne in

mind, the diagnosis of advanced abdominal malignancy with peritoneal and pleural metastases is often made. This error was made in the one case not operated upon which terminated fatally. Despite the fact that the lesion is pathologically benign, the patients are often very cachectic.

Bomze and Kirshbaum [3] stressed the almost magical relief which removal of the pelvic tumor offers even in grave cases. Harris and Meyer [4] stated that it was of utmost importance that internists and surgeons alike be made cognizant of these facts, for otherwise the occasional patient exhibiting this syndrome might be doomed as hopeless or inoperable. Finally, Glass and Goldsmith [6] warned that it behooved both the clinician and the pathologist to exercise extreme caution in making a prognosis in cases in which a pelvic mass was associated with ascites and hydrothorax.

The mechanism of the formation of the hydrothorax and ascites is still obscure despite many theories. Meigs,[2] in his review, ruled out tuberculosis, carcinomatosis, protein deficiency, and anatomic communication between the pleural and peritoneal cavities as the possible etiological factors. Although he stated that no cause had been proved, he considered Selye's alarm reaction as the best explanation offered. Selye had shown that repeated trauma to peritoneum of rats caused resistance to be built up against the traumatic agent. However, after one to three months of continuous irritation, the animals lost their resistance and succumbed with symptoms of anaphylactic shock and with the accumulation of pleural and peritoneal transudates. Harris and Meyer [4] suggested that a "toxic substance from the tumor may damage the capillary and lymphatic endothelium and that the pressure of the tumor may obstruct the lymphatic channels."

Bomze and Kirshbaum [3] suggested that "it is possible that in a patient who has a subclinical cardiac weakness with low reserve, the added stress thrown on the heart by the pressure of a heavy ovarian fibroma combined with the possible interference with pelvic and lower abdominal circulation may produce low grade decompensation resulting in ascites and pleural effusion." However, Glass and Goldsmith [6] pointed out that repeated thoracentesis did not prevent reaccumulation of the pleural fluid, while removal of the pelvic mass resulted in complete reabsorption of the transudate. They concluded that the decompensation theory did not adequately explain the formation of the effusion. The normal arm to tongue circulation time and venous pressure noted in our patient, while there was still evidence of pleural effusion, lends further evidence against this theory. The etiology is still as obscure as it was in 1937, when Meigs and Cass [1] admitted that it was impossible to give a logical etiological explanation for the development of the effusion.

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HEREDITARY ECTODERMAL DYSPLASIA *

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RECENTLY we have had occasion to observe a family which exhibited some of the clinical characteristics of hereditary ectodermal dysplasia. These characteristics have been described in detail by other authors.[1, 2, 3, 4, 5, 6, 7, 8, 9] Therefore, we wish to limit this presentation to case reports and a brief discussion of this interesting and rare anomaly. Of this family of seven children, four manifested definite evidences of this defect.

CASE REPORTS

Case 1. Mrs. R. D. P., aged 25, a white female, was admitted to the Department of Medicine, Hutchinson Memorial Clinic on October 24, 1941. The chief complaint was bronchial asthma and allergic rhinitis of three months' duration.

Past History: From infancy the patient had the type of nails to be described under physical examination. Tonsillectomy was performed at the age of three. The patient had had scarlatina at the age of eight. Three years prior to admission she had had an attack of "bronchitis" similar to the present episode. She had had intermittent rhinitis since that time.

Family History: The father died at the age of 56 years; the mother was living and well. The father had normal nails and teeth, but had abnormally thin hair and "peculiarly" shaped ears.

Siblings: Corolie—normal except for thyroid hypofunction.
Inez—died at 7 months with abnormal nails.
Louis—patient described below as Case 2.
Isabella—normal except for thin hair.
Boy—lived 36 hours and was said to present no ectodermal abnormalities.
Francis—patient described below as Case 3.
Henry—living and well.
Rosalie—patient described as Case 1.

* Received for publication June 22, 1942.
From the Department of Medicine, School of Medicine of Tulane University of Louisiana and Charity Hospital of Louisiana, New Orleans, Louisiana.

Physical Examination: Blood pressure 110 mm. Hg systolic and 75 mm. diastolic; pulse 82; respirations 18; temperature 98.6° F. The patient was an alert young brunette who was apparently in good general health. Her jaw was abnormally prominent for a woman.

The hair was black in color, fine in texture and sparse. Despite the fact that the patient had not had a haircut in 12 years, the length of the longest individual hairs did not exceed 20 cm. There were no localized areas of alopecia. Eyebrows appeared normal. Eyes, ears, nose, and mucous membranes of the pharynx revealed no abnormalities. Consultation with the dentist revealed no clinical evidence of third molars. The thyroid gland was not enlarged. There was no adenopathy of the cervical lymph glands.

FIG. 1. Dystrophy of nails. Case 1.

The lungs revealed no abnormal findings except musical râles in the left base. The heart was normal. The mammary glands appeared to be composed of normal breast tissue. The areolae and nipples were normal in appearance.

The abdomen and extremities were negative except for changes in the nails of the feet and hands. The nails were short, not extending to the edge of the nail bed. They were thin and brittle and presented a central concavity. The ends of the digits appeared to be flattened, and did not show a normal contour (figure 1).

Laboratory Data: Feces, urine and blood revealed no abnormalities. The basal metabolic rate was reported as —26 on November 11, 1941, and as —23 on December 6, 1941. Glucose tolerance test (Exton Rose technic) revealed a fasting blood sugar of 90 mg. per cent, 30 minutes 153 mg. per cent, and 60 minutes 108 mg. per cent.

Plates of the skull revealed a normal sella turcica and roentgenograms of the lungs were negative.

Biopsy of the skin revealed a normal distribution of sweat and sebaceous glands.

Case 2. Mr. L. D., brother of Case 1, reported to Hutchinson Memorial Clinic at our request. The patient considered himself in perfect health, there being no complaints. Past history was irrelevant.

Physical Examination: Temperature 98.7° F.; blood pressure 130 mm. Hg systolic and 82 mm. diastolic; pulse 96; respirations 20. The patient was a 36 year old white radio engineer who appeared to enjoy excellent health.

The skin appeared thinner than normal, slightly transparent, and white. Sparseness of the hair was considered to be abnormal for his age, but there were no localized areas of alopecia. Examination of the teeth revealed an absence of the upper third molars, and an impacted upper right cuspid. The remainder of the physical examination was essentially negative save for the abnormalities of nails.

The nails were similar to his sister's in appearance, the degree of involvement being greater, however.

Laboratory findings were noncontributory. The basal metabolic rate was reported as ± 0. Glucose tolerance (Exton Rose) fasting 105 mg.; 30 minutes, 48 mg.; 60 minutes, 200 mg. The urine revealed 1 + reducing substance.

Case 3. Mr. F. D., aged 22, was seen through the courtesy of the physicians of the Marine Hospital, New Orleans, Louisiana. At the time of the examination, he was being studied for enuresis which developed during service in the United States Coast Guard. He exhibited findings identical with those of his brother.

Glucose tolerance test revealed a normal curve in every respect.

Employing a direct measurement [10] of water loss from the surface of the skin in these patients it was found that the water loss was normal when they were in a comfortable environment. When the temperature and humidity of the room were elevated to 95° F. and 75 per cent relative humidity they increased their rate of water loss in a normal fashion. The areas studied included finger tips, toe tips, forearm, epigastrium and forehead. Details of these studies [11] will be reported at a later date. These data indicate that sensible and insensible perspiration in these three patients were normal.

To our knowledge these are the first quantitative observations of the functional state of the sweat apparatus in patients suffering from hereditary ectodermal dysplasia.

Discussion

Tissues deriving their origin from ectoderm which may be involved in this dysplasia are the skin, mucous membranes of the mouth, nose and anus, the sweat glands, sebaceous glands, lacrimal glands, salivary glands, hair, teeth, nails, breasts, endocrines and central nervous system. When it is considered that any tissue of ectodermal origin may be affected, it is readily understood that numberless combinations may arise.

Usually the chief tissue affected is the skin. It may be observed to be thin, glossy, transparent, and parchment like. In some patients hyperpigmentation has been described. The dysplasia may involve the sweat glands and pilosebaceous glands so that there may be a complete absence of sweating. This anhidrosis may actually lead to hyperthermias as a result of dysfunction of the heat regulatory mechanism.

The mucous membranes have been reported as showing atrophic changes especially in the form of atrophic rhinitis and dysphasia.

Cases have been described in which there was impairment of lacrimal secretion, and disturbance of the sensation of taste and smell.

In a few of the reported cases, abnormalities of the ears have been noted. They have been described as being of different configuration on both sides, pointed at the tops in some cases, and have at times stood out obliquely from the head.

Patients invariably show a varying degree of defective growth of hair not only on the head but elsewhere on the body. Typically, the hair is fine, uniformly sparse, and may even be totally absent. The eyebrows usually show similar changes, particularly the inner one-third. Faulty dentition is a frequent finding in this condition. The teeth may be few in number, prone to early decay, malarranged, and the deciduous teeth may be kept for abnormal periods of time.

Characteristically, the nails show abnormalities of shape and color. There is concavity and depression of the central body of the nail, giving them a "spoon" shaped appearance.

The mammae often show rudimentary development or may be absent. There is evidence to show the endocrine glands are also involved. Thannhauser [12] reported a case of the anhidrotic type which presented what he regarded as symptoms of adrenal medullary insufficiency, associated with abnormalities of bones of the skull. Barrett [13] reported a family showing abnormalities of the hair and nails, and hypothyroidism which involved three generations. We are impressed with the objective similarity between hereditary ectodermal dysplasia and a case of idiopathic hypoparathyroidism reported by Emerson [14] and his associates of a 15 year old school boy who showed thin patchy hair, sparse eyebrows and lashes, dry skin, irregularly developed teeth, and nails which were short and thick. The skin and hair changes were considered to be "multiple congenital ectodermal defects." This patient had laboratory findings consistent with the diagnosis of hypoparathyroidism.

Very few gross anatomical changes of the central nervous system have been noted. Stammering and stuttering have been observed in some cases. Wechselmann and Loewy [15] drew attention to diminution of intellect in one of their cases. Barrett [13] also emphasized abnormalities of a mental or nervous type in the family reported by him. These changes in mentality are by no means a constant finding. On the contrary, it seems to be rarely associated with this dysplasia.

Defects of non-ectodermal origin involving the osseous system have been noted, particularly in the anhidrotic type. Prominence of the supraorbital ridges and flattening of the nasal bones have frequently been referred to.

It has been suggested [12] that two main clinical syndromes may be ascribed to this dysplasia. One is found in males, is transmitted by females, and is characterized by defective sweating, sparseness of hair, and abnormal dentition. The other appears in both sexes and is transmitted by either sex. This latter form is marked by dystrophies of the hair and nails.

Conclusion

A family of individuals in Louisiana exhibiting the clinical manifestations of hereditary ectodermal dysplasia is reported.

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11. BURCH, G. E., and SODEMAN, W. A.: To be published.
12. THANNHAUSER, S. J.: Hereditary ectodermal dysplasia of the anhidrotic type, Jr. Am. Med. Assoc., 1936, cvi, 908.
13. BARRETT, A. M.: Hereditary occurrence of hypothyroidism with dystrophies of the nails and hair, Arch. Neurol. and Psychiat., 1919, ii, 628.
14. EMERSON, K., WALSH, F. B., and HOWARD, J. E.: Idiopathic hypoparathyroidism, a report of two cases, ANN. INT. MED., 1941, iv, 1256.
15. WECHSELMANN, W., and LOEWY, A.: Untersuchungen, an drei blutverwandten Personen mit ektodermalen Hemmungsbildungen besonders des Hautsdrüssen-systems, Berl. klin. Wchnschr., 1911, xlviii, 1369.

EDITORIAL

THE ETIOLOGY OF PRIMARY ATYPICAL PNEUMONIA

A TYPE of pneumonia differing significantly in its clinical features from that of pneumococcal and other recognized bacterial origin has recently been described by a number of investigators (e.g., Reimann,[1] Longcope,[2] Dingle and Finland[3]). This has usually been designated as acute pneumonitis, virus pneumonia or primary atypical pneumonia.

The onset is usually more gradual than in pneumococcal pneumonia, with progressively increasing fever, malaise, a non-productive "rasping" cough, headache which may be severe, and sometimes nausea and abdominal discomfort. Rarely is there a chill, pleural pain, herpes, or bloody or rusty sputum. The fastigium is usually reached after four or five days. There is usually a relative bradycardia. In milder cases there is little disturbance of respiration, but in severe ones there may be marked prostration, tachycardia, severe cough with tenacious mucoid sputum, tachypnea, dyspnea, cyanosis and even asthmatic attacks.

The infection usually terminates by lysis after seven to 10 days, but in severe cases it may persist for three weeks or more. They may be a secondary rise in temperature. Convalescence may be protracted and accompanied by prostration which seems out of proportion to the severity of the infection. The course of the disease is not influenced by the sulfonamides, but the mortality is low.

Abnormalities on physical examination are usually slight. A little injection of the pharynx, limited areas of slight dullness, enfeebled breath sounds and fine moist râles may be demonstrated. These are often transient and shifting. In severe cases such changes are more marked and wide-spread. Roentgenograms show changes in the lungs much more extensive than might be expected, consisting of patchy areas of consolidation extending out from the hilum or diffusely scattered in one or both lower lobes, or in the severe cases widely disseminated. These shadows may persist for some time after the temperature has fallen.

At the onset the leukocyte count is normal or even reduced, but there is often a late leukocytosis. Blood cultures have been negative in uncomplicated cases, and cultures and inoculations of sputum have revealed no organisms of significance. Peterson et al. have reported the development of "cold" autohemagglutinins during convalescence.

Very few adequate postmortem studies have been reported. These have shown scattered, deep red, moist areas of consolidation. Microscopically

[1] REIMANN, H. A.: An acute infection of the respiratory tract with atypical pneumonia. A disease entity probably caused by a filtrable virus, Jr. Am. Med. Assoc., 1938, cxi, 2377–2384.

[2] LONGCOPE, W. T.: Bronchopneumonia of unknown etiology (variety X): a report of thirty-two cases with two deaths, Bull. Johns Hopkins Hosp., 1940, lxvii, 268–305.

[3] DINGLE, J. H., and FINLAND, M.: Virus pneumonias. II. Primary atypical pneumonia of unknown etiology, New England Jr. Med., 1942, ccxxvii, 378–385.

the alveoli contained a loose exudate consisting of mononuclear cells, red blood cells, and fibrin but no pus cells. The alveolar septa were thickened by swelling of the epithelium, edema and some infiltration with mononuclear cells.

There is no sound basis for assuming that this is a "new" disease. Descriptions of similar clinical syndromes may be found in the early literature. The apparent increase in frequency during the past five years and the wide-spread awareness of the condition naturally stimulated many attempts to determine its etiology. The suggestion that it is a virus infection was based in part on the failure to demonstrate any bacterial agent and also on similarities to other infections known to be caused by filtrable viruses, particularly psittacosis. In fact, in a limited number of cases of primary atypical pneumonia, viruses have been isolated which are closely related antigenically to the psittacosis virus.

In 1940 Meyer reported the isolation of a psittacosis-like virus from the blood of a woman who had been exposed to pigeons. An identical virus was obtained from five birds of this flock. Meyer and his associates [4] have shown that viruses closely related to psittacosis and to the meningopneumonitis virus of Francis and Magill are widely diffused among pigeons and poultry in this country. They cited 10 cases of atypical pneumonia in man which could be traced to exposure to pigeons. In some cases a virus was obtained from the sputum, but they point out that in most cases proof that the virus was contracted from the birds was not complete.

Stickney et al.[5] reported isolating a similar virus from a single case of atypical pneumonia by intranasal inoculation of mice. The man had been exposed to wild pigeons.

Beck and Eaton [6] reported a study of four strains of virus isolated from human cases by intranasal inoculation of mice. One proved to be identical with the meningopneumonitis virus. The other three were identical with one another and antigenically were related to but not identical with the viruses of meningopneumonitis, psittacosis and lymphogranuloma venereum. Unlike the viruses to be discussed later, they caused the development of inclusion bodies in the brain and lungs of infected mice. Because of the rarity with which such viruses were obtained from patients with atypical pneumonia (3 out of 122 cases) and because of the small percentage (10 to 15) of patients who gave a positive complement fixation reaction with psittacosis antigen, Eaton concluded that viruses of the psittacosis type can be responsible for only a small proportion of cases of atypical pneumonia.

In most cases attempts to demonstrate the nature of the infectious agent of primary atypical pneumonia by direct experiment met a serious obstacle

[4] Meyer, K. F., et al.: Ornithosis in pigeons and its relation to human pneumonitis, Proc. Soc. Exper. Biol. and Med., 1942, xliii, 609.

[5] Stickney, J. M., and Heilman, F. R.: The isolation of a virus in atypical pneumonia, Proc. Staff Meet. Mayo Clin., 1942, xvii, 369–375.

[6] Beck, D., and Eaton, M. D.: Identification of two strains of virus isolated from cases of atypical pneumonia, Jr. Infect. Dis., 1942, lxxi, 97–101.

in the fact that all the usual experimental animals, including the white mouse, ferret, hamster and monkey, are insusceptible to infection, even when serial intranasal inoculations are carried out. Stokes, Kenny and Shaw in 1939 reported infecting mice and guinea pigs with material from two human cases, but the agent was lost before its nature or possible significance could be demonstrated.

In 1942 Blake et al.[7] reported the occurrence of four cases of atypical pneumonia in a family whose cats had suffered a severe acute respiratory infection clinically resembling the catarrhal type of feline distemper. Sputum from one patient on intranasal inoculation caused infection and pneumonia in two cats primarily inoculated, but it was not possible to maintain the infection in series. A strain was obtained from one sick cat which showed high virulence and was carried through a series of four cats. It could not be transmitted to mice. Attempts to demonstrate neutralizing antibodies for this virus in the serum of convalescent human patients gave inconclusive results.

Slightly later Baker[8] reported a study of a virus obtained from cats during the same epidemic period, which he could maintain in mice and transmit back to cats. Elementary bodies resembling those of psittacosis were found. Using these as antigen he carried out complement fixation tests with serum from a small series of human cases and obtained positive reactions with smaller quantities of serum than with his normal controls. No neutralization tests were reported. The relationship of these feline viruses to other known viruses was not reported. The evidence that they were the cause of human infections is inconclusive.

Weir and Horsfall[9] were probably the first to bring convincing evidence of the isolation of a virus from patients with this disease syndrome. After many unsuccessful attempts with other animals, they succeeded in infecting the mongoose by intranasal inoculations in a series of animals using sputum and nasal washings from four patients living in three widely separated areas in the state of New York. They demonstrated that the agent passed through a Berkefeld filter, and that it could be cultivated on the chorio-allantoic membrane of a chick embryo. Following recovery, the animal was immune to reinfection, and its blood acquired the power of neutralizing the virus. The convalescent serum of four patients from widely separated localities also neutralized the virus, although their serum obtained during the acute stage of the disease did not do so. By crossed neutralization tests they demonstrated that the four strains of virus isolated were identical, but were different from influenza A virus. Although crossed neutralization tests with other viruses were impracticable, because of differences in pathogenicity and

[7] Blake, F. G., et al.: Feline virus pneumonia and its possible relation to some cases of primary atypical pneumonia in man, Yale Jr. Biol. and Med., 1942, xv, 139–166.

[8] Baker, J. A.: A virus obtained from a pneumonia of cats and its possible relation to the cause of atypical pneumonia in man, Science, 1942, xcvi, 475–476.

[9] Weir, J. M., and Horsfall, F. L., Jr.: The recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose, Jr. Exper. Med., 1940, lxxii, 595–610.

for other reasons they believe the agent is different from the viruses of meningopneumonitis, psittacosis, lymphocytic choriomeningitis and Rift Valley fever.

Because the importation of the mongoose into the United States is prohibited, the work had to be done in Jamaica, and it was not practicable to carry it out with these animals on a more extensive scale. In 1943, however, Horsfall et al.[10] reported further studies of cases of atypical pneumonia based upon experiments with cotton rats. They had noted in their previous work that mongooses which had survived infection and acquired an immunity to this virus also showed an immunity to the pneumonia virus of mice. This they attribute to the presence of a common antigen in the two viruses, although there are other clear cut differences between them. By intranasal inoculation of cotton rats, they obtained from 12 cases of primary atypical pneumonia an agent which stimulated a similar heterologous immunity to the pneumonia virus of mice, although it did not produce any gross lesions which could be reproduced in serial passages. This agent was filtrable, it could be maintained by serial passages in cotton rats and could be cultivated in a chick embryo.

They obtained sputum from one human case which caused pneumonia in 78 per cent of cotton rats primarily inoculated, although the infection could not be maintained by serial inoculations. Using this sputum as an infecting agent, they found that the sera from six of 11 convalescent patients tested neutralized the virus completely, whereas serum from normal human beings and from patients in the acute phase of primary atypical pneumonia had no protective power. Serum from all the 11 convalescent cases tested neutralized the agent responsible for stimulating the production in cotton rats of antibodies to the pneumonia virus of mice. Such sera did not neutralize the virus of mouse pneumonia, psittacosis, lymphocytic choriomeningitis or influenza A and B. However, the serum of rats which had recovered from infection with human virus or cultures of virus in chick embryos neutralized both the agent in the sputum and the pneumonia virus of mice. The authors concluded that the 12 strains of virus recently isolated in cotton rats are probably identical with or closely related to the mongoose virus, and that the agent is responsible for many of the cases of atypical primary pneumonia in man.

In 1942 Eaton et al.[11] obtained a virus by intranasal inoculation of sputum into cotton rats under ether anesthesia. With material from 17 of 78 human cases tested, pulmonary lesions were produced on primary inoculation, and six of these could be maintained by serial passages in rats with an increase in virulence. The adapted strains were also pathogenic for hamsters. The agent was filtrable. No inclusion bodies were demonstrated. Rats after

[10] Horsfall, F. L., Jr., et al.: A virus recovered from patients with atypical pneumonia, Science, 1943, xcvii, 289–291.

[11] Eaton, M. D., et al.: An infectious agent from cases of atypical pneumonia apparently transmissible to cotton rats, Science, 1942, xcvi, 518–519.

recovery were immune to reinoculation. All six strains were identical antigenically. Serum of hyperimmunized animals neutralized the agent. However, serum of rats after recovery from a single inoculation and convalescent human serum afforded only partial or irregular neutralization. Therefore the evidence that the agent is the cause of the most common type of atypical pneumonia they regarded as inconclusive.

Finally Rose and Molloy [12] succeeded in infecting recently weaned guinea pigs by intranasal inoculation of sputum or other infectious material from seven of 11 cases of human infection. In five cases serial passages were required. With the adapted strain they were also able to infect cotton rats. The agent was filtrable. The pneumonic lesions resembled those described in human cases. No inclusion bodies were found. Animals after recovery from any strain were immune to reinfection with all the strains, which appeared to be identical antigenically. They were unable to demonstrate neutralizing antibodies in the serum of either convalescent animals or human cases. However, repeated intranasal inoculation of either cotton rats or guinea pigs with infectious human material rendered them immune to the passage strains.

This necessarily incomplete review indicates that primary atypical pneumonia is not a disease entity from the etiological standpoint, but a clinical syndrome which may be caused by any one of several different agents. The evidence that some cases are caused by viruses related to that of psittacosis seems fairly conclusive, but these appear to constitute only a small proportion of the whole group. The same is true of the still smaller number of cases caused by the virus of lymphocytic chorio-meningitis and by the rickettsia of Q fever. The significance of the other viruses discussed is somewhat less clear, although the evidence that they were the cause of the infection in the human cases is strong.

The virus isolated by Horsfall in the mongoose seems the most firmly established because of the successful neutralization tests with convalescent serum. Failure to demonstrate neutralizing power, however, does not exclude a virus as a causative agent. No published data were found to indicate whether or not the viruses isolated by the last three groups of investigators are identical or closely related. If this proves to be the case, the significance of this work is manifestly increased. Neither is their relationship to other known viruses entirely established. It seems probable, however, that they do not belong in the psittacosis group because of differences in pathogenicity as well as their failure to excite formation of inclusion bodies. More investigation is needed to decide these questions, but lack of susceptible animals makes the problem difficult.

[12] Rose, H. M., and Molloy, E.: Observations concerning the etiology of primary atypical pneumonia, Science, 1943, xcviii, 112–114.

REVIEWS

Pancreatic Function and Pancreatic Disease Studied by Means of Secretin. By HENRIK O. LAGERLÖF, M.D. With a foreword by JOSEPH H. PRATT, M.D. Translated by HELEN D. FREY. 289 pages; 23.5 × 15 cm. The Macmillan Company, New York. 1943. Price, $3.50.

The exhaustive studies by Lagerlöf and his associates on the functional diagnosis of both acute and chronic disease of the pancreas are the basis for this comprehensive résumé. The monograph is divided into five sections, each of which consists of several chapters. Part I includes a review of the early work of pancreatic secretion and a discussion of methods for the collection and analysis of duodenal contents. Part II covers the anatomy of the pancreas, etiology and symptomatology of acute and chronic pancreatitis together with a discussion of various aids for differential diagnosis. Part III is an evaluation of the secretin test in normal and pathologic states. Parts IV and V are devoted to general discussion and case histories. There is no subject index, but a very detailed table of contents facilitates finding the material on specific subjects. This volume should prove to be of value to every student of gastroenterology and to all who are interested in the study of pancreatic disease.

M. A. A.

Biological Symposia. Volume X: Frontiers in Cytochemistry. Edited by NORMAND L. HOERR, Henry Wilson Payne Professor of Anatomy, School of Medicine, Western Reserve University. Eighteen Contributors. 334 pages; 25 × 17.5 cm. Jaques Cattell Press, Lancaster, Pennsylvania. 1943. Price, $3.50.

This volume consists of the papers in an expanded form that were presented at a symposium held at the University of Chicago in honor of Dr. R. R. Bensley. Seventeen investigators besides Dr. Bensley have discussed various aspects of cytochemistry. The importance and ever increasing potentialities of this field in the study of normal and abnormal cellular function become more and more apparent as one reads the various chapters. This monograph should be useful to anyone working in cytochemistry and open new avenues of thought to those engaged in related research.

M. A. A.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Notes for the R.M.O. of an Infantry Unit. By C. P. BLACKER, M.C. (M.A., M.D., F.R.C.P.). General Editor: THE RT. HON. LORD HORDER, G.C.V.O. 77 pages; 17 × 11 cm. 1943. Oxford University Press, New York. Price, $1.50.

White Blood Cell Differential Tables. By THEODORE R. WAUGH, B.A., M.D., C.M. 126 pages; 18.5 × 12.5 cm. 1943. D. Appleton-Century Company, New York. Price, $1.60.

Elements of Medical Mycology. By JACOB HYAMS SWARTZ, M.D. Foreword by FRED D. WEIDMAN, M.D. 179 pages; 22 × 15 cm. 1943. Grune & Stratton, Inc., New York. Price, $4.50.

Behind the Universe. By LOUIS BERMAN, M.D. 303 pages; 21 × 14.5 cm. 1943. Harper & Brothers, New York. Price, $2.75.

Metabolism Manual. By JESSIE K. LEX, R. T., M. T., (ASCP). 56 pages; 23.5 × 15.5 cm. 1943. The Waverly Press, Baltimore, Maryland. Price, $1.75.

Soviet Health Care in Peace and War. By ROSE MAURER. 48 pages; 21.5 × 14 cm. 1943. The American Russian Institute for Cultural Relations with the Soviet Union, Inc., New York. Price, $.10.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,501 Fellows and Associates of the College on active military duty. Herewith are reported the names of 83 additional members, bringing the grand total to 1,584.

Horst A. Agerty
Forrest N. Anderson
John J. Archinard
Philip K. Arzt

Russel L. Baker
Lewis Barbato
Wayne C. Barnes
Julian R. Beckwith
William O. Benenson
Louis J. Benton
Edward W. Boland
George A. Boylston
Lewis H. Bronstein
Lewis W. Brown

Hayes W. Caldwell
Joseph L. Campbell
Samuel Candel
Howard C. Coggeshall
Felix H. Crago

Lucious L. Davidge
John P. Davis
Vincent P. Del Duca
Charles N. Duncan
John L. Dyer

Herbert Eichert
Mackinnon Ellis
David E. Engle

Stanley Fahlstrom
John L. Ferry
A. James French
Mervyn J. Fuendeling

Delmar R. Gillespie
J. S. Golden
Edward D. Greenwood
Morris B. Guthrie

George C. Ham
Percy G. Hamlin
Bain L. Heffner

Ng William Hing

Edward R. Janjigian

J. Allen Kennedy
John J. Keveney

Frederick L. Landau, Jr.
Richard P. Laney
John A. Layne
Henry J. Lehnhoff
Robert S. Liggett
Leo W. Lloyd

Isaac H. Manning, Jr.
Thomas W. Martin
Francis J. McEvoy
George T. McKean
Robert H. Mitchell
Raymond W. Monto
Joseph E. Muse, Jr.

Louis Ochs, Jr.

Paul B. Patton
Elmus D. Peasley
Carey M. Peters
Michael Peters
Heyes Peterson

Samuel T. R. Revell, Jr.
Edward S. Ross
Maurice J. Rotkow

William Saphir
Sidney Scherlis
Eugene M. Schloss
Carl A. Schuck
Arthur F. Schultz
Leonard B. Shpiner
Hyman U. Solovay
Mitchell A. Spellberg
Charles F. Stone, Jr.
Stuart Dos Passos Sunday
Boen Swinny

Ray Vander Meer
Raymond G. Vinal

George W. Warrick
Samuel J. Weinberg

Forrest M. Willett
Paul R. Wilner
Walter H. Wilson
Robert M. Woods

New Life Member of the College

Dr. Paul F. Stookey, F.A.C.P., Kansas City, Mo., has subscribed to Life Membership and his initiation fee and Life Membership subscription have been added to the permanent Endowment Fund of the College.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Wesley W. Spink, F.A.C.P., Minneapolis, Minn.—"Sulfanilamide and Related Compounds in General Practice" (Second Edition).

Reprints

Dr. Irene V. Allen (Associate) East Saint John, N.B., Can.—1 reprint;
Dr. Arthur Bernstein, F.A.C.P., Newark, N. J.—1 reprint;
George R. Callender, F.A.C.P., Colonel, (MC), U. S. Army—1 reprint;
Dr. Harold R. Carter (Associate), Denver, Colo.—1 reprint;
Dr. Raymond O. Muether, F.A.C.P., St. Louis, Mo.—20 reprints;
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—2 reprints;
Walter L. Voegtlin (Associate), Lieutenant Commander, (MC), U. S. Naval Reserve —9 reprints.

At the 72nd Annual Meeting of the American Public Health Association in New York City, October 12, 1943, the Sedgwick Memorial Medal "for distinguished service in Public Health" was awarded to Brigadier General James Stevens Simmons, F.A.C.P., Director of The Preventive Medicine Division, Office of The Surgeon General, U. S. Army.

Major General John M. Willis, (MC), U. S. Army, Fellow of the American College of Physicians, heretofore stationed at Camp Grant, Ill., has been transferred to command all medical and hospital services of the Army throughout the Ninth Service Command, including California, Nevada, Utah, Arizona, Oregon, Washington, Idaho, Montana and Colorado. He will have direct supervision over such institutions as the Fitzsimons General Hospital, Denver, and the Letterman General Hospital, San Francisco.

General Willis has been a medical officer of the regular Army since 1911. His new headquarters will be at Fort Douglas, Utah.

Dr. Harry P. Thomas (Associate), formerly with the Austin (Tex.) State Hospital, recently became Assistant Superintendent of the Woodmen of the World War Memorial Hospital at San Antonio, Tex.

Dr. D. O. N. Lindberg, F.A.C.P., formerly Medical Director and Superintendent of the Macon County (Ill.) Tuberculosis Sanatorium, accepted the appointment as Superintendent and Medical Director of Buena Vista Sanatorium, Wabasha, Minn., and assumed duties on December 5, 1943.

Dr. Cornelius O. Bailey, F.A.C.P., Los Angeles, Calif., was appointed Surgeon General of the Military Order of the World War at its recent national convention held in Cincinnati. Dr. Bailey will carry on the work begun by Colonel Joseph Heller, a distinguished physician who was recommended for a medal of honor for his work under gunfire in the Philippines.

The University of Pennsylvania Receives Fund for Research in Physical Medicine

The establishment of the first center for the scientific study and development of physical medicine as a branch of medical practice was announced on December 14, 1943, by Mr. Basil O'Connor, President of The National Foundation for Infantile Paralysis. The center will be in the Graduate School of Medicine of the University of Pennsylvania, Philadelphia. The National Foundation for Infantile Paralysis has made a grant totaling $150,000 for a five-year period beginning January 1, 1944.

In making the announcement, Mr. O'Connor stated that this is one of the most important steps yet taken by The Foundation and that it will not only advance the treatment of infantile paralysis, but many other diseases. He said that today there are only a few schools or departments connected with any of the medical training centers which are equipped to explore thoroughly on a sound scientific basis the possibilities of physical medicine.

The Center for Research and Instruction in Physical Medicine will include:

1. A center for development of physical medicine as a scientific part of the practice of medicine.
2. A training center for medical leaders and teachers in this branch of medicine.
3. A school for training technical workers under the guidance of such professional and scientific leadership, such a school to be only incidental to and dependent upon the first two purposes.

General direction will be assigned to Dr. Robin C. Buerki, Dean of the Graduate School of Medicine.

"Affiliated Units," U. S. Office of Civilian Defense

In early December, the U. S. Office of Civilian Defense announced that 93 hospitals and medical schools scattered throughout the country have completed formation of "affiliated units" of civilian physicians, which will be available to either OCD or the Army in the event of need for setting up emergency hospital facilities in their respective areas. Each unit is composed of 15 physicians, surgeons and other specialists, and forms a balanced professional staff. They will be used to supplement the staffs of emergency base hospitals located in relatively safe zones on the fringes of critical areas, in case it is necessary to transfer civilian patients to these hospitals because of emergency in such areas.

The units will be called upon by the War Department to staff extemporized hospitals should there be a sudden influx of battle front casualties, or some other extraordinary military necessity, requiring hospitals and physicians beyond the immediate capacity of the Army in any particular locality. They will be used for military

emergency purposes only in or near the communities in which the staff resides. Their duty will be temporary and they will be replaced by Army doctors as quickly as the Surgeon General of the Army can make necessary assignments.

Normally, all the 15 doctors of a unit are associated with a single hospital. Each unit includes: a chief and assistant chief of medical services, two general internists, a chief and assistant chief of surgical services, four general surgeons, two orthopedic surgeons, one dental surgeon, one pathologist and one radiologist.

Physicians accepted for service in the units receive inactive reserve commissions in the U. S. Public Health Service, but will be called to active duty only at the request of OCD. When a unit is needed, either to staff an emergency base hospital or to assist the Army temporarily in a military emergency, the physicians of the unit will be placed on active duty for the duration of that particular emergency. Approximately 100 such units have already been completed.

Report, North Carolina Regional Meeting

Dr. Paul F. Whitaker, F.A.C.P., Kinston, N. C., College Governor for that state, reports upon a regional meeting of the College for North Carolina held at the Bowman Gray School of Medicine, Winston-Salem, October 29, 1943. The program of the meeting was published in a previous issue of this journal. The meeting was one of the most successful ever held in North Carolina. There were present forty Fellows and Associates and eight visitors from the armed forces, many medical students, members of the resident staff of The Baptist Hospital, and faculty members of the School of Medicine. The reception of the program was most favorable.

At the banquet in the evening seventy-seven were present. Dr. J. W. Vernon, F.A.C.P., President of the North Carolina Medical Society, Dr. George Carrington, F.A.C.S., First Vice President of the North Carolina Medical Society, and Dr. Arthur Grollman, F.A.C.P., Professor of Research Medicine, were among those present. Dr. Wingate M. Johnson, F.A.C.P., was the Toastmaster and addresses were made by Dr. Hartwell Cocke, First Vice President of the College and Dr. Paul F. Whitaker. The highlight of the banquet session was the address of the guest speaker, Dr. William B. Castle, F.A.C.P., Professor of Medicine at Harvard Medical School, whose title was "As They Were (Colored Pictures of Australia and the East in 1938)."

Governor Whitaker appointed a committee consisting of Dr. W. B. Dewar, F.A.C.P., Raleigh, Dr. Thomas Baker, F.A.C.P., Charlotte, and Dr. W. R. Berryhill, Chapel Hill, to arrange a College regional meeting for the state in 1944 at Chapel Hill.

Central Committee on Post-War Medical Service

The Central Committee on Post-War Medical Service, consisting of official committees appointed by the American College of Physicians, the American College of Surgeons and the American Medical Association, will meet at the Statler Hotel, Washington, D. C., January 14, 1944, at 9:30 a.m. The A. C. P. Committee consists of Dr. Walter Palmer, F.A.C.P., Chairman, New York City, Commander Edward L. Bortz, F.A.C.P., Philadelphia, Dr. William B. Breed, F.A.C.P., Boston, and Dr. George Morris Piersol, F.A.C.P., Philadelphia.

War-Time Graduate Medical Meetings

The Committee on War-Time Graduate Medical Meetings, headed by Commander Edward L. Bortz, Chairman, their offices at 4200 Pine St., Philadelphia, Pa.,

is now publishing a monthly bulletin of the latest developments of their teaching programs and as a supplement of the brochure recently distributed. The United States is divided into twenty-four zones or regions and the fundamental organization of courses is similar in all zones. It is felt that an exchange of ideas by the various zones will be helpful and that each will profit by the others' experience.

These monthly bulletins not only give a schedule of programs held during the preceding month, but give the schedule of meetings for the future. Interested physicians and medical officers may have their names put on the mailing list on request to Commander Bortz.

War-Time Graduate Medical Meetings consist of clinics, demonstrations, lectures, panel and round table discussions and ward round teaching, and are conducted on request for the medical staff of Army and Navy hospitals throughout the United States. The program has been marked with phenomenal success and received with great appreciation. Space does not permit our reproducing here the many excellent programs that have been given or are scheduled for the future. Significant among the programs is that organized for Zone No. 5, of which Dr. James Alexander Lyon, F.A.C.P., Washington, D. C., is the Chairman. His is a very carefully organized, extensive program for eleven hospitals, eight from the Army and three from the Navy, with a medical personnel of approximately 750 officers. Dr. Lyon's program covers ninety-one lectures, or other type of presentations, requiring the services of ninety-eight speakers.

Bulletin No. 2 of the Central Committee, published December 15, 1943, discloses completed plans for meetings during January at the Station Hospital, Indiantown Gap, Pa., at the Naval Hospital, Philadelphia, Pa., at Fort Monmouth, N. J., at various Army and Navy hospitals in Maryland, the District of Columbia, Virginia and West Virginia, at the Naval Hospital at Annapolis, at Camp Shanks, Orangeburg, N. Y., and elsewhere.

Memorial Room to Dr. Trask

Yale University School of Medicine, New Haven, dedicated a room to the memory of the late Dr. James D. Trask, Phillips' Medalist of the American College of Physicians in 1922. Funds were contributed by medical students, alumni of the pediatric service of the New Haven Hospital and by associates and friends of Dr. Trask.

University of Florida Graduate School of Medicine

Dr. Turner Z. Cason, F.A.C.P., Jacksonville, is Director of the new Graduate School of Medicine of the University of Florida. The tentative program for developing this department calls for eleven sections. Dr. William C. Blake, F.A.C.P., Tampa, will head the Section on Internal Medicine and Dr. Lucien Y. Dyrenforth, F.A.C.P., Jacksonville, will head the Section on Pathology. A staff of instructors, all certified by their specialty boards, will serve with the chairman. The State Medical Association and the State Board of Health will coöperate with the University of Florida.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered the annual Walter L. Niles Memorial Lecture at Cornell University Medical College, October 19, 1943, on "The Neuropsychiatry of Global War." The lecture is given annually in memory of Dr. Niles, a former Fellow of the American College of Physicians and a former Dean of the Medical College at Cornell.

Colonel George C. Dunham, F.A.C.P., (MC), U. S. Army, has been appointed Executive Vice President of the Institute of Inter-American Affairs.

Dr. Eugene M. Landis, F.A.C.P., Boston, has been elected a member of the Council on Pharmacy and Chemistry of the American Medical Association.

Friends and colleagues of Dr. David J. Davis, F.A.C.P., who retired recently as Dean of the University of Illinois College of Medicine, have established the D. J. Davis Lectureship on Medical History in his honor.

MEDICAL KNOWLEDGE EXCHANGED BETWEEN U. S. AND AMERICAN REPUBLICS

Dr. Eugene P. Campbell, F.A.C.P., Director of the United States missions assisting El Salvador, Costa Rica, Honduras, Guatemala and Nicaragua in health and sanitation problems, recently reported that medical men from the United States are going to these republics working on tropical diseases in hospitals for periods of three weeks. They then go with a field party for a week or ten days to observe at first-hand more about malaria, dysentery and other tropical diseases. "The exchange of physicians and technicians among the Americas is an important phase of the program of inter-American coöperation which resulted from the conference of American Foreign Ministers at Rio de Janeiro in January 1942," according to a report from the American Medical Association. Among members of our College who have completed training in Central America are: Dr. John W. Scott, F.A.C.P., Associate Professor of Clinical Medicine, University of Alberta Faculty of Medicine, Edmonton; Dr. Robert C. Lowe (Associate), Assistant Professor of Medicine, Louisiana State University School of Medicine, New Orleans; Dr. Thomas H. McGavack, F.A.C.P., Associate Professor of Medicine, New York Medical College, New York City; Dr. Wesley W. Spink, F.A.C.P., Clinical Associate Professor of Internal Medicine, University of Minnesota Medical School, Minneapolis; and Dr. Harry F. Dowling, F.A.C.P., Clinical Professor of Medicine, George Washington University School of Medicine, Washington, D. C.

Dr. Frank J. Milloy, F.A.C.P., and Dr. Jesse D. Hamer, F.A.C.P., both of Phoenix, Ariz., have been chosen Editor and Associate Editor, respectively, of Arizona Medicine, the new journal to be published by the Arizona State Medical Association.

Dr. Robert H. Bayley, F.A.C.P., and Dr. Louis A. Monte, F.A.C.P., have been promoted to Associate Professor of Medicine and Clinical Associate Professor of Medicine, respectively, on the medical faculty of the Louisiana State University.

Dr. Richard Bardon (Associate), Duluth, has been elected Vice President of the Northern Minnesota Medical Association.

Dr. Richard E. Shope, A. C. P. Phillips' Medalist, 1937, a member of the Rockefeller Institute for Medical Research, recently received the John Scott Medal and "premium" of $1,000 awarded by the Directors of City Trusts, Philadelphia, for his "discovery of the complex etiology of swine influenza."

John Scott, an Edinburgh chemist, bequeathed to the City of Philadelphia in 1816 the sum of $4,000, the income of which shall be "laid out in premiums to be

distributed among ingenious men and women who made useful inventions." Little is known of the donor, or of the reason for his selecting Philadelphia; however, the fund has grown to more than $100,000.

Dr. Oscar O. Miller, F.A.C.P., Louisville, was elected President-Elect of the Kentucky State Medical Association at its annual meeting in October.

Dr. Malcom T. MacEachern, F.A.C.P., Chicago, has been appointed Chairman of the Council on International Relations, created by the American Hospital Association to coöperate with Nelson Rockefeller, coördinator of the Office of Inter-American Affairs.

A.C.P. Will Hold "Limited" Annual Meeting, 1944

At a meeting of the Board of Regents of the American College of Physicians at Philadelphia, November 20, 1943, a resolution was adopted providing that the College shall hold an annual meeting during March or April of 1944, without a specific scientific program, but with a regular annual business meeting, as provided in the By-Laws, and meetings of the Board of Regents and the Board of Governors. The time and place of the meeting was left for settlement to President James E. Paullin, to Executive Secretary E. R. Loveland and to Secretary General George Morris Piersol.

At this meeting will be held the election of Officers, Regents and Governors of the College, and other College business will be transacted. Inasmuch as it was felt highly important that a full complement of the Board of Regents and of the Board of Governors be present, a further resolution was adopted providing that their travel expenses be defrayed by the College. The full discussion appears in the Minutes of the Board of Regents, published in this issue.

OBITUARIES

DR. WILLARD J. STONE

With the death of Dr. Willard J. Stone on October 30, 1943, the medical profession of Southern California lost one of its outstanding internists.

Dr. Stone was born May 31, 1877, at Gloversville, New York. His premedical training was received at Union College, Schenectady. He chose the University of Michigan for his medical training, acquiring the degree of B.Sc. in 1899 and that of M.D. two years later. Following his graduation he was able to broaden the scope of his medical knowledge by experience gained during a sojourn in Europe of three years, two of which were spent at the University of Vienna and one at University College, London.

On his return to the United States he made his home in Toledo, Ohio, and during the eleven years that he remained there, he established himself as a most competent specialist in internal medicine, occupying the position of Attending Physician at St. Vincent's Hospital for several years and that of Physician-in-Chief at Flower Hospital, Toledo, for eleven years, and building up a very extensive private practice. During World War I, Dr. Stone served as Chief of Medical Service at the U. S. Army Base Hospital at Fort Riley, Kansas.

After the war Dr. Stone settled in Pasadena, California, where he became well known, both for his indefatigable zeal in the pursuit of his profession and his ability as a diagnostician and internist. He was for many years Clinical Professor in Medicine at the University of Southern California Medical School and Attending Physician at the Collis P. and Howard Huntington Memorial Hospital. He was a member of the Los Angeles County Medical Association, the California Medical Association, the Los Angeles Academy of Medicine, the American Medical Association, the American Society for Clinical Investigation, and the American Climatological and Clinical Association. He was also Fellow of the American College of Physicians. In the midst of all these activities, Dr. Stone found time to make two worthy contributions to medical literature as the author of "Bright's Disease and Arterial Hypertension" and "Blood Chemistry Colorimetric Methods."

Dr. Stone passed away at his office at the close of a busy day.

ROY E. THOMAS, M.D., F.A.C.P.,
Governor for Southern California

DR. EUGENE LEROY HORGER

Dr. Eugene Leroy Horger, F.A.C.P., Columbia, South Carolina, died of coronary thrombosis on October 22, 1943, at the age of 54. Dr. Horger was born in Orangeburg County, South Carolina, April 26, 1889. He graduated from Wofford College in 1910, entered the University of Maryland

School of Medicine and received his M.D. Degree in 1914. Thereafter, he served as Resident Pathologist at the University of Maryland Hospital for a year, when he removed to Columbia, South Carolina, to become Assistant Physician and Pathologist to the South Carolina State Hospital. He served this institution for the balance of his life, having been, successively, Senior Assistant physician and Pathologist, Acting Superintendent and Instructor in Mental Nursing, and, finally, Clinical Director.

Dr. Horger was Honorary Lecturer in Mental Disorders, School of Social Work, University of South Carolina, and was Neuropsychiatric Examiner at the South Carolina Penitentiary. He was also an Associate in Psychiatry at the Medical College of the State of South Carolina. He had served as Vice-President of his county medical society and as President of his state medical society. For many years he was Associate Editor of the Journal of the South Carolina Medical Association. In addition, he was a member of the Southern Medical Association, American Psychiatric Association and Tri-State Medical Association. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1935.

KENNETH LYNCH, M.D., F.A.C.P.,
Governor for South Carolina

DR. CHARLES WESLEY MARTIN

Dr. Charles Wesley Martin, F.A.C.P., of Woodmere, Long Island, New York, died at the Nassau Hospital on November 16, 1943, of bronchopneumonia. He was born in Perth Amboy, New Jersey on October 6, 1895.

Dr. Martin attended Wesleyan University and Columbia University. He received a B.S. and M.S. degree from Columbia and graduated from the College of Physicians and Surgeons of Columbia University in 1921. Following graduation he completed internships at the Post-Graduate and Babies Hospitals in New York City.

He has practiced as a pediatrist in Woodmere and Nassau County for twenty years. During this time he has been active in private practice, on various hospital staffs and in the County Medical Society. He was President of the Nassau County Medical Society in 1941 and was a past president of the Rockaway Medical Society. At the time of his death he was a vice president of the Second District Branch of the State Medical Society. For several years he was connected with the New York Post-Graduate Medical School as Associate in Pediatrics.

At the time of his death Dr. Martin was a Consultant in the Diseases of Children at the Meadowbrook, Long Beach and Mercy Hospitals and an attendant at the Nassau, St. Josephs and South Nassau Communities Hospitals. He was a Fellow of the American Medical Association, a Fellow of the American College of Physicians and the American Academy of Pediatrics,

a member of the Brooklyn Pediatric Society, and a Diplomate of the American Board of Pediatrics.

Dr. Martin is survived by his wife, Mrs. Berla Henderson Martin, and three children, Jane, Robert and Caryl.

As a pioneer in the specialty of Pediatrics in Nassau County, as a devoted and enthusiastic member of various hospital staffs and as an individual, exemplifying the best in Medicine, he will be greatly missed in Nassau County.

BENJAMIN R. ALLISON, M.D., F.A.C.P.

DR. RALPH K. UPDEGRAFF

Dr. Ralph K. Updegraff, F.A.C.P., Cleveland, Ohio, was born in that city on March 30, 1873. He received his preliminary education in the local schools, later attended the Case School of Applied Science, and then was graduated from the Western Reserve University School of Medicine in 1902.

Dr. Updegraff enjoyed a large practice in internal medicine. He was active in both civic and medical affairs. He was formerly an instructor and associate in Physical Diagnosis at Western Reserve University School of Medicine. At the time of his death, he was a member of the staffs of the Cleveland City and St. Lukes Hospitals, and had served since 1916 as Director of Medicine at St. John's Hospital.

Dr. Updegraff was a member of his county and state medical societies and of the American Medical Association. He was a former President of the Cleveland Academy of Medicine. He had been a Fellow of the American College of Physicians since 1922, and was a Diplomate of the American Board of Internal Medicine.

He died at Wilmington, Delaware, July 13, 1943, of coronary occlusion.

A. B. BROWER, M.D., F.A.C.P.,
Governor for Ohio

DR. RALPH R. HENDERSHOTT

Dr. Ralph R. Hendershott, Tiffin, Ohio, was born in 1876. He received his medical education at the Starling Medical College, later merged with the Ohio State University, graduating in 1898.

Dr. Hendershott was an active general practitioner, and became an Associate of the American College of Physicians by virtue of membership in the American Congress on Internal Medicine, when that organization was merged with the College in 1926. He was highly interested in State and National affairs. He had been President of the Seneca County (Ohio) Medical Society, Councillor of the Ohio State Medical Association for five years and served as its President in 1935. Earlier, 1916, he was President of the North Western Medical Association.

Dr. Hendershott served in World War I as a Captain in the Medical Corps of the United States Army. He had a large personal following, both

in and out of the profession. His death occurred on May 1, 1943, as a result of coronary occlusion. His passing is a great loss to his community.

A. B. Brower, M.D., F.A.C.P.,
Governor for Ohio

DR. PETER WHITMAN ROWLAND

Dr. Peter Whitman Rowland, University, Mississippi. Born, Oakland, Mississippi, February 25, 1861, son of Dr. William Brewer Rowland and Mary Judin Bryan Rowland. He died in his sleep at his home, October 14, 1943. Educated in private schools up to the age of 18; Memphis Hospital Medical College (now the University of Tennessee), 1882; postgraduate work at New York Polyclinic Medical School and the University of Chicago; since 1903, Professor of Pharmacology, University of Mississippi School of Medicine; Field Director, Rowland Medical Library, University of Mississippi; former President, Mississippi State Medical Association; former member of the Mississippi State Board of Health; member, North Mississippi Medical Society, Tri-State Medical Association, Southern Medical Association and American Medical Association, Fellow of the American College of Physicians since 1931; diplomate, American Board of Internal Medicine.

The Rowland Medical Library of the University of Mississippi, named in his honor, became a success through his untiring efforts. Probably the greatest single contribution Dr. Rowland made to science was his discovery of the value of deeply implanted use of oxygen in cases of lobar pneumonia. On May 12, 1942, the Mississippi State Medical Association awarded him a certificate of recognition "for the first clinical use, in 1903, of therapeutic oxygen by catheter deeply implanted in the nasopharynx to mitigate the anoxia of lobar pneumonia, wherefore, he merits this recognition of priority for such an accomplishment." Dr. Rowland was active up to the time of his death. He was greatly beloved by all who knew him.

John G. Archer, M.D., F.A.C.P.,
Governor for Mississippi

MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 20, 1943

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters in Philadelphia, November 20, 1943, at 10:00 a.m., with President James E. Paullin presiding, with Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

James E. Paullin ..... *President*
Ernest E. Irons ..... *President-Elect*
Charles H. Cocke ..... *First Vice President*
A. Comingo Griffith ..... *Third Vice President*
William D. Stroud ..... *Treasurer*
George Morris Piersol ..... *Secretary-General*
David P. Barr
J. Morrison Hutcheson
Walter W. Palmer
O. H. Perry Pepper
T. Homer Coffen
Jonathan C. Meakins
Hugh J. Morgan
Charles F. Tenney
Reginald Fitz
Charles T. Stone
William B. Breed
Paul W. Clough ..... *Acting Editor*, ANNALS
Edward L. Bortz ..... *Chairman, Advisory Committee on Postgraduate Courses and Chairman of the War-Time Graduate Medical Meetings*

The Secretary read abstracted Minutes of the preceding meeting of the Board of Regents, April 4, 1943, which, by resolution, were approved.

PRESIDENT JAMES E. PAULLIN: I would like to say that since the last meeting of the Board of Regents there were two policies which were formulated at that time and which have gone on to a most successful fruition. One is the wonderful piece of work which has been done by Dr. Bortz in the establishment of the War-Time Graduate Medical Meetings. I am extremely anxious that everyone secure some of those brochures which he has prepared, because I have had many requests for them. That is really a most remarkable accomplishment, and what has been done thus far is only the beginning. The second thing is the work which Dr. Palmer, Chairman of our Committee on Post-War Planning, is doing, in coöperation with similar committees from the American College of Surgeons and the American Medical Association. I feel that our own Committee, under the leadership of Dr. Palmer, can interest itself in another phase of post-war planning that to a considerable extent will concern our own membership—which we shall discuss at length later in the meeting.

Of course you all know about the Regional Meetings, on which there will be a report later in this meeting, but I would like you to believe and to know that the activities of the College, since our last meeting, have been toward the accomplishment of a definite end, perhaps to as fertile a period, if not more so, than any other period

in the existence of the College. So far as I know this has been due altogether to the activities of these various committees.

Will the Secretary kindly present the communications?

The Secretary read the following communications:

(1) Dr. James F. Churchill, F.A.C.P., Regent—containing regrets at being unable to be present;

(2) Dr. Gerald B. Webb, F.A.C.P., Regent—containing regrets at being unable to be present;

(3) Dr. Howard T. Karsner, F.A.C.P., Cleveland—a report on his attendance as the official delegate of the American College of Physicians to a celebration of the one hundredth anniversary of the School of Medicine of Western Reserve University at Cleveland on October 27, 1943;

(4) A communication for the records stating that at the last meeting of the Board of Regents a limited number of Fellows and Associates were reported as delinquent in dues for two or more years and subject to be dropped from the Roster, according to the By-Laws, but adding that each of these had subsequently paid his delinquent dues with the exception of two, who were dropped from the Roster "as of June 30, 1943";

(5) Dr. Wallace M. Yater, F.A.C.P., member of the Credentials Committee and Governor of the College for the District of Columbia—a proposal that certification by the appropriate board be made a requirement for Associateship in the College, and that the requirements for elevation to Fellowship be expanded to include the preparation and submission of a thesis on some medical subject, or the satisfactory report of some original investigative work;

(6) Dr. J. Russell Verbrycke, Jr., F.A.C.P.—a suggestion that the College incorporate a system of seniority members;

(7) Dr. Willard O. Thompson, F.A.C.P.—two communications; one attesting to the great possibilities of an extension of the postgraduate program of the College through short courses, and one a request of approval for members of the faculty of the College course in "Endocrinology" at Chicago to write up their lectures and presentations for publication in the Journal of Clinical Endocrinology;

(8) Dr. James D. Bruce, F.A.C.P., Regent—regrets at being unable to attend the meeting, and the recommendation that the resumption in full measure of the Annual Session of the College be deferred, that a limited meeting for organizational and business purposes be held, and that the Regional Meeting program continue for the period of the War;

(9) Dr. Raymond B. Allen, Executive Dean, University of Illinois—commendation of the College program of short Postgraduate Courses, such as the one in "Endocrinology" in Chicago during October, 1943, with a recommendation that this successful experiment be expanded, and with the cordial offer of coöperation on behalf of the University of Illinois.

PRESIDENT PAULLIN: Gentlemen, you have heard these communications. It seems to me the one from Dr. Yater concerning certification as a prerequisite for Associateship might be referred to the Committee on Credentials for investigation and report back to this Board; that the communication concerning the numbering of members by length of service might be referred to the Committee on Public Relations; that the communication from Dr. Thompson, concerning the publication of his clinics, might be referred to the Committee on the ANNALS OF INTERNAL MEDICINE for report.

(A motion was made, seconded and unanimously carried, embodying the suggestions of the President.)

PRESIDENT PAULLIN: Next is the report of the Secretary-General, Dr. George Morris Piersol.

SECRETARY-GENERAL GEORGE MORRIS PIERSOL: We report the deaths, since the last meeting of this Board, of 31 Fellows and 5 Associates, as follows:

Fellows

Abbott, William Osler	Philadelphia, Pa.	September 10, 1943
Ashley, Claude Wilber	Bloomsburg, Pa.	May 22, 1943
Barker, Lewellys Franklin	Baltimore, Md.	July 13, 1943
Beam, Hugh A.	Moline, Ill.	April 29, 1943
Borden, Frank Runcorn	(MC), USA (Retired)	March 28, 1943
Brown, Orville Harry	Arcadia, Calif.	July 26, 1943
Brush, Arthur Conklin	New York, N. Y.	March 17, 1943
Connor, Guy Leartus	Detroit, Mich.	April 19, 1943
Dana, Harold Ward	Brookline, Mass.	May 8, 1943
Davis, Arthur E.	Scranton, Pa.	May 2, 1943
Davis, Stirley Casper	Tucson, Ariz.	March 14, 1943
Dorsey, John Lanahan	Baltimore, Md.	September 15, 1943
Funk, William Harris	(MC), USN	January 7, 1943
Gormly, Charles Francis	Providence, R. I.	June 26, 1943
Greene, Irving Waterloo	Owosso, Mich.	June 28, 1943
Haines, Edgar Fremont	(MC), USA	July 22, 1943
Hoge, Albert Hammond	Bluefield, W. Va.	April 9, 1943
Lohman, William Henry	Brooklyn, N. Y.	August 8, 1943
McElroy, James Bassett	Memphis, Tenn.	March 24, 1943
Milliken, Herbert Eldridge	Surry, Maine	February 9, 1943
Mooney, Robert C	Washington, D. C.	October 4, 1943
Morrissey, Frank Beattie	St. Paul, Minn.	June 16, 1943
Rowland, Peter Whitman	University, Miss.	October 14, 1943
Shelby, Edmund Pendleton	Venice, Fla.	September 22, 1943
Sloan, Andrew	Utica, N. Y.	April 21, 1943
Stone, Willard John	Pasadena, Calif.	October 30, 1943
Updegraff, Ralph Kinsey	Cleveland, Ohio	July 13, 1943
Waddell, Charles Walter	Fairmont, W. Va.	March 29, 1943
Wall, John Cox	Eastman, Ga.	May 18, 1943
Watkins, John Taylor	Detroit, Mich.	May 8, 1943
Wolfsohn, Julian Mast	San Francisco, Calif.	July 1, 1943

Associates

Collie, Roy Munro	Schenectady, N. Y.	April 24, 1943
Hendershott, Ralph Reid	Tiffin, Ohio	May 1, 1943
Lake, George B.	Waukegan, Ill.	March 2, 1943
Overton, William Simmons	Binghamton, N. Y.	May 17, 1943
Phillips, Robert Titus	Portland, Maine	June 11, 1943, while a prisoner at a Japanese Camp

We report the following 9 additional Life Members, since the last meeting of this Board, making a grand total of 220, of whom 25 are deceased, leaving a balance of 195:

Seymour Fiske	New York, N. Y.
Herbert T. Kelly	Philadelphia, Pa.
Archibald L. Hoyne	Chicago, Ill.
Edgar P. McNamee	Cleveland, Ohio
John R. Van Atta	Albuquerque, N. M.
H. Sheridan Baketel	Jersey City, N. J.
Harold Guyon Trimble	Oakland, Calif.
Constantine P. Faller	Harrisburg, Pa.
Russell Lowell Sands	Santa Monica, Calif.

(On motion, seconded and unanimously carried, the report of the Secretary-General was received and filed.)

PRESIDENT PAULLIN: Next are the Committee reports and new business. The first will be that of the Executive Secretary, Mr. Loveland.

MR. E. R. LOVELAND: This report for the year 1943 outlines briefly our work this year, and will undoubtedly be amplified by Committee Chairmen in their reports.

Membership: The College membership, exclusive of action to be taken today, consists of:

Masters	4
Fellows	3,874
Associates	1,109
	4,987

The years are beginning to tell, for the losses from death are rather large. From now on we may expect even greater losses from death. Few indeed of our early members of 1915–16–17 remain.

The number of candidates for membership has been somewhat affected by the War. For instance:

	Candidates		
	Fellows	Associates	Total
1941	368	317	685
1942	386	324	710
1943	288	239	527

However, there appears to be an increasing number of inquiries concerning admission requirements.

Employees: My assistant, Mr. Hegland, resigned July 9, 1943, to accept an appointment as Executive Secretary of the Chicago Dental Society, obtaining a three-year contract and a 50 per cent increase in salary. For the period of the War, or certainly for the present, we do not propose to ask for another assistant, per se, to succeed Mr. Hegland. We propose to distribute greater responsibilities among each of our staff and "to carry on."

The War has brought many problems to us from the standpoint of employees. War industries and big wages have lured away several of our stenographers, and I am having to train new ones. I believe we now have a fairly stable and competent staff, and that their ability and loyalty will grow the longer they are with us.

Roster: At the direction of President Paullin, after consulting with the Executive Committee of the College, seven of whom definitely and fully approved, a Roster of the College membership was published this summer and distributed last month. We need not describe this because each of you has received your copy. It includes the entire membership of the College up to date and indicates all of those who are serving in the Armed Forces. After all, it is similar to the College Directory, except it does not contain biographical data about the members. As an interim publication, it has been well received and will serve a useful purpose. The cost of the Roster was about $1,200.00, $700,00 of which was not budgeted.

Regional Meetings: During the year 1943 thirteen official Regional Meetings have been held, covering all parts of the United States (also some parts of Canada), excepting California, Nevada, Arizona, New Mexico, Utah, Colorado, North Dakota, South Dakota and Minnesota. There have been in attendance at these meetings some 2,800 physicians, of whom 1,500 were members of the College. The Central Office has coöperated with each one, publishing their programs, promoting their publicity and handling many of the business and financial details. Your Secretary

has attended the majority of them. The President, President-Elect, First Vice President, Dr. Bortz, Dr. Piersol, and others, have also attended some of these meetings as the official Officers of the College. This activity has been more appreciated, has been more conducive to continued interest in the College, has produced a continuing number of candidates for membership, and has promoted more effectively the good will of the College throughout the Country than any other single activity. The cost, however, will have exceeded the budget appropriation probably by $1,000.00. Our budget was $3,500.00, and we anticipate the total cost of these Regional Meetings for the year to be about $4,500.00. We believe, however, it has been a very good investment.

Annals of Internal Medicine: The ANNALS has come through the year really with flying colors. A year ago we anticipated a sharp decline in circulation, and, therefore, in income. We expressed the intention of working vigorously toward building up circulation through non-members and also in attempting to increase the volume of advertising and the advertising income. It is true that our member circulation was greatly decreased, because of 1,500 members who are on active military duty, whose dues were waived. We were delighted, however, to find so many of them who wished to subscribe and they were accorded the $6.00 reduced courtesy rate. Furthermore, we succeeded in obtaining a large number of direct subscribers among physicians and institutions, and the Surgeons General of the Army and Navy have sent in subscriptions for a large number of their posts, both at home and overseas. The result is that our income from subscriptions has decreased but little. May I add that we have been successful in increasing materially our advertising volume with a result that the advertising income increased more than $1,000.00 this year?

Postgraduate Courses: During 1943 the College conducted six Postgraduate Courses, with a gross attendance of 407, of whom 300 were members of the College and 107 were non-members. Details about these courses will later be reported by Dr. Bortz. The cost to the College was about $600.00.

Fellowships and Awards: During the year there were no new Research Fellowships or Awards granted, but two of our former Research Fellows have completed their work, and you will hear later from that Committee on the results.

War-Time Graduate Medical Meetings: The College has furnished the office space and other facilities to this Committee, and has made a great contribution to its work through the large number of Governors and Regents participating and through coöperation. Details will be received later from Dr. Bortz, the Chairman.

Board of Governors: Our Board of Governors have been active and coöperative. We regret that a few of the Governors have not yet been inspired to organize Regional Meetings in the Southwest, but we think this will come. I am sure there have been special problems which they felt were insurmountable. In one instance, Colorado, our Governor has applied all of his energies to the War-Time Graduate Medical Meetings, and has done an excellent job. He has not had any time remaining to work on Regional Meetings for the College.

Finances: The income of the College for 1943 will have exceeded our budget anticipations by some $15,000.00. This is due to a larger income from investment, a materially larger income from the Annals and a very much larger income from Life Memberships. We have 33 new Life Members this year, with a subscription of $7,905.00. This is far beyond our fondest expectations, for we estimated the income from this source would be only $2,500.00. The College will have operated below its budget by over $6,000.00.

In conclusion, I want to express again, as I have so many times before, my appreciation of the ever ready assistance and coöperation of all the Regents, Governors and Committeemen. It is always a growing pleasure and inspiration to administer the College responsibilities.

PRESIDENT PAULLIN: Gentlemen, you have heard the report of the Executive Secretary. Are there any questions that you would like to ask? If not, a motion for its adoption is in order.

(A resolution was unanimously adopted to accept and file the report.)

PRESIDENT PAULLIN: Next is the report of the Committee on Credentials, Dr. George Morris Piersol, Chairman.

DR. PIERSOL: At a meeting of the Committee on Credentials, at which all members were present, November 19, 1943, the credentials of 188 candidates for Fellowship and 165 candidates for Associateship were reviewed. In the hands of the Regents have been placed the list of names. The names of candidates not recommended for election at this time have been crossed off. On the Fellowship list will be found the names of 11 candidates who have been marked for recommendation for election to Associateship rather than direct Fellowship, as proposed by their sponsors.

The Committee recommends to the Board of Regents the election of the following:

For Advancement to Fellowship as of this date	112
For Advancement to Fellowship "as of the spring, 1944"	1
For Direct Election to Fellowship as of this date	13
	126
For Election to Associateship	138
	264*

An analysis of the candidates for Fellowship is as follows:

Recommended for Advancement	113
Recommended for Direct Fellowship	13
	126†
Recommended first for Associateship	11
Recommended for Deferment	41
Recommended for Rejection	10
	188

An analysis of the candidates for Associateship is as follows:

Recommended for Election	127‡
Recommended for Deferment	1
Recommended for Rejection	37
	165

* Of this total, 113 are advancements to Fellowship; therefore, only 151 are new names on the College Roster.

† 67 per cent.

‡ 77 per cent.

I move, Mr. President, that the following 126 candidates shall be approved for election to Fellowship: (List was published in the December, 1943, issue of this journal).

(The motion was duly seconded from the floor. There was brief discussion concerning a few of the candidates. It was brought out that General Norman Thomas Kirk is an orthopedic surgeon, but as Surgeon General of the U. S. Army, our By-Laws provide that he shall serve, regardless of the type of his medical practice, as a member of the Board of Governors of the College, and, therefore, must be a Fellow. It was also pointed out that some of the candidates not on the recommended list

had as yet failed to complete certification; such certification is required of Associates elected after April 6, 1940. There was no further discussion. The motion was put to vote and unanimously carried, and the election of the candidates was ordered by the President.)

DR. PIERSOL: An analysis of the group of 196 Associates elected five years ago, December 18, 1938, is as follows:

Advanced to Fellowship	164	(83.7%)
Deceased	3	
Dropped for Failure to Take Up Election	1	
Dropped for Delinquency	1	
Resigned	1	
Rejected	4	
Dropped for Failure to Present Credentials	8	
Time Extended for Qualification, due to military service	14	
	196	

I move, Mr. President, that the following list of 138 candidates be approved for election to Associateship: (List was published in the December, 1943, issue of this journal).

(The motion was seconded by Dr. Walter W. Palmer, and unanimously carried, and the President declared the list of candidates elected to Associateship.)

On motion by Dr. Piersol, seconded by Dr. Palmer and unanimously carried, the names of twelve Associates who had failed to qualify for Fellowship within the maximum five-year period were dropped from the Roster, in accordance with the By-laws.

Dr. Piersol read the names of fourteen Associates whose maximum five-year terms under ordinary circumstances would now expire, but who because of active military service will be granted additional time after the War to complete Fellowship requirements. He further reported that the Executive Office has a careful routine so that all Associates are kept informed of the period that still remains in which to qualify for Fellowship. For two years prior to the end of their Associateship terms, they are systematically circularized and given every opportunity to present their credentials.

DR. J. MORRISON HUTCHESON: I move, Mr. President, that the report of the Chairman of the Committee on Credentials be approved as a whole.

(The motion was duly seconded from the floor. There was no discussion. It was carried unanimously and was so ordered by the President.)

PRESIDENT PAULLIN: Next is the report of the Committee on the ANNALS OF INTERNAL MEDICINE, Dr. Walter W. Palmer.

DR. WALTER W. PALMER: From a business standpoint, the report is excellent as may be seen in the Treasurer's report. The surplus for the year is slightly over $10,000.00. Mr. Loveland reports a steady increase in circulation in spite of the waiving of dues of members in service and discontinuing the Annals. By vigorous efforts, subscriptions from institutions and non-member physicians have been obtained. For Volumes XVII–XVIII, circulation was 5,708, as compared with 5,670 for Volumes XV–XVI. The advertising has been increased by the amount of $1,000.00. The page reduction has met Government regulations ten per cent. By Government regulation the weight of paper used must be reduced from the present sixty pound to forty-five pound, but this will not affect the ANNALS until April, 1944, owing to stock on hand. The Acting Editor will comment on material for the ANNALS.

(A motion was made, seconded and unanimously carried, that the report of the Committee on the ANNALS OF INTERNAL MEDICINE be adopted and filed, and it was so ordered by the President.)

PRESIDENT PAULLIN: Next we shall have a report from the Acting Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Paul W. Clough.

DR. PAUL W. CLOUGH: I have little to add. We have reduced somewhat the size of the Volume, so that each of the two Volumes coming out in 1943 will contain approximately 1,050 pages of scientific matter. This excludes advertising. It compares with about 1,200 to 1,250 pages during the first half of 1942. As you know, we brought out two special numbers—one on medico-legal topics and one devoted exclusively to papers delivered before the Regional Meetings of the College. I should like to obtain at this time an expression on the part of the members of the Board of Regents as to how they feel about these numbers. We have been giving some consideration to getting out another Regional Meeting number, although we think the feeling of the Committee on the ANNALS is somewhat dubious about the advisability of doing this. As far as material is concerned, it has held up in quantity fairly well, although I think the quality has dropped off somewhat. That is to say, I think that a smaller portion of the papers received contain notable contributions. We have accepted now for publication, sixty-five major articles, including fourteen Regional Meeting papers (the latter being, perhaps, more suitable for a special number than for a regular number) as compared with eighty manuscripts a year ago. We still have about fifty accepted case reports, which are ample to run for at least a year. There are also about thirty articles that have not been finally passed upon, of which, perhaps, half will be finally acceptable. So, we are fairly well provided with material.

As far as the Regional Meeting papers are concerned, there is a minority composed of high-class papers, which we would be glad to put in under any circumstances. There is a substantial number of papers which really make no original contribution, but which are, in many cases, excellent reviews, which probably have definite value as an educational medium, but we cannot accept all papers of that type. Many are largely duplications of papers which have been given previously. Then, there is another group of these papers which are obviously gotten together hastily, and show it; they are really not suitable for publication. I estimate that we have rejected about half of these papers which have been submitted for publication. This naturally creates a little feeling on the part of the authors. The Executive Secretary has been careful to say that he would like to have Regional Meeting papers presented "for consideration," but in many cases the authors expect them to be accepted, and they feel disappointed, if not actually disgruntled, when their papers are not accepted.

As far as the selection of papers in general is concerned, my policy has been as follows: first, I read them all carefully; my associate, Dr. Halsey Barker, reads them and we try to come to an independent opinion. If we agree, we usually accept or reject the paper forthwith. If there has been a difference of opinion, or if we are in doubt, we try to get some third person, preferably one who is especially familiar with that field of medicine, to read them. I have thus far hesitated to inflict any of these papers upon the Associate Editors, partly because of the delay that will ensue and partly because of the fact that I know these men are overburdened with other things, and it would be more or less of an imposition to submit any considerable number of papers to them. I might say, however, that, as Acting Editor, I will be only too glad to receive any criticisms, or suggestions, or to receive any help that is available, as far as passing judgment on individual papers is concerned. I have occasionally imposed upon Dr. Palmer already.

PRESIDENT PAULLIN: You have heard the report of the Editor. Are there any comments or discussion?

DR. PALMER: I feel quite strongly that we should publish less, if necessary, rather than reduce our standard, because it takes a long time to build up a reputation, and you can destroy it in one number.

DR. CHARLES H. COCKE: I found the medico-legal number tremendously interesting; I think there is some very valuable material in it that ought to have been of record. I am grateful to Dr. Clough for publishing this.

(On motion by Dr. A. Comingo Griffith, seconded by Dr. J. Morrison Hutcheson, and unanimously carried, the Editor's report was adopted.)

PRESIDENT PAULLIN: Next is the report of the Committee on Advertisements by George Morris Piersol, Chairman.

DR. PIERSOL: A meeting of the Committee on Advertisements was held at the College Headquarters, Thursday, September 30, 1943, with Dr. George Morris Piersol, Chairman, Dr. Charles C. Wolferth and the Executive Secretary, Mr. E. R. Loveland, present. Dr. Sydney R. Miller, the third member of the Committee, was unable to be present, but it was provided that a full report be sent him.

Advertisements in recent issues of the ANNALS were all carefully scanned, and it was the unanimous opinion that they were all entirely appropriate, and, actually, the advertising as a whole was on a higher scale than that of most other medical journals. The Committee saw no objection to the advertisements being consolidated chiefly in the front section of the journal, due to the fact that practically all advertisers request a location in the front form.

Advertising for the ANNALS was classified roughly in the following divisions:

(*a*) Sanatoria Advertisements

The advertisements of Sanatoria as a class are considered acceptable. There could be no objections raised to accepting advertisements from reliable and ethically operated sanatoria, but it was pointed out that probably few members of the College refer patients to sanatoria, and thus few sanatoria will be interested in placing contracts.

(*b*) Equipment.

Under this heading is included x-ray apparatus, blood pressure apparatus, metabolism equipment, office furniture and fixtures, files, etc. As a group there is no problem concerned in the acceptance of this type of advertising, because each one will be considered individually on its merits and on the standing and methods of the manufacturer.

(*c*) Drugs and Pharmaceuticals.

The present requirements are that no drug may be accepted for advertising in the ANNALS unless it has been formally accepted by the Council on Pharmacy and Chemistry of the American Medical Association. A partial examination of the list of pharmaceuticals so excluded from the ANNALS showed that there are many recognized and approved drugs, already widely used and proved efficacious, that under the present rule may not be advertised in the ANNALS. A further examination disclosed that well recognized medical journals, such as the American Journal of the Medical Sciences, the Southern Medical Journal, many of the State medical journals and practically all of the special journals, outside of those published by the American Medical Association, accept the advertising of many of these drugs not yet "Council accepted." Very few private journals adhere fully to the Council requirements.

It was moved, seconded and carried that the Committee on Advertisements shall recommend to the Board of Regents, at its next meeting, November 20, that the present rule concerning drug advertisements be rescinded, and that the Board of Regents authorize the Committee on Advertisements to exercise its judgment in the acceptance of drug advertisements in the ANNALS in the future. The Committee suggested that one of the principles to be followed shall be not to accept for advertising any product that has been submitted to the Council but rejected. Therefore,

the Committee would be called upon to pass upon advertisements submitted for drugs either already "Council approved" or as yet never submitted to the Council, and each advertisement would be individually considered.

(*d*) Foods.

The Committee was inclined to consider favorably only those food advertisements which have a specific propriety, such as baby foods, diabetic preparations, etc., and that foods in general, such as special brands of orange juice or pineapple juice, or the usual run of canned vegetables or fruits would not be considered appropriate and particularly dignified for advertising in this journal.

(*e*) Vitamin Products.

Vitamin products properly are classified with drugs, because in general they are subject to approval by the Council on Pharmacy and Chemistry.

It was the opinion of the Committee that all advertising of Vitamin Products should be especially carefully examined, and only the recognized better products making no undue claims be accepted by the College for advertising.

The consensus was that all advertising irrelevant to the practice of Internal Medicine and its allied specialties probably should not be accepted for the ANNALS. This refers to cigarettes, automobiles and many other miscellaneous advertising that is often seen in other medical journals.

The Committee reviewed two specific advertising contracts submitted for 1944, among which there were several pharmaceuticals that had not yet been submitted to the Council on Pharmacy and Chemistry, and action was deferred, pending the action of the Board of Regents.

We submit this report, and the only recommendation on which the Committee would like action, one way or another, is the recommendation in regard to drug advertisements—whether the ironclad rule of the present that no pharmaceuticals except "Council accepted" preparations be advertised be rescinded and the acceptance of advertisements left to the judgment of this Committee.

(The following motion was made by Dr. A. C. Griffith and seconded by Dr. J. Morrison Hutcheson:

RESOLVED, that the present rule concerning drug advertisements in the ANNALS be rescinded and that the Board of Regents authorize the Committee on Advertisements to exercise its judgment in the acceptance of drug advertisements in the future.)

(This motion was opened for discussion and there was long and detailed debate on the advantages or disadvantages of the present regulations providing that the Committee on Advertisements may accept only "Council approved" products for advertising in the ANNALS OF INTERNAL MEDICINE. Dr. Palmer felt that some manufacturers make use of the condition, "not yet submitted to the Council," in an attempt to break down the standards of the Council. Dr. Irons strongly objected to the adoption of the above resolution and urged the College to support the Council. Dr. Pepper pointed out that there is no financial reason why the College should want to increase its advertising particularly, and said that "a drug that has not yet been sent to the Council on Pharmacy and Chemistry is either so new that we shouldn't advertise it, or so old that it should have been sent to the Council." He urged that the College continue to uphold the Council and to maintain the highest standards of any journal in the country. Dr. Piersol said that the present rule is ideal, so far as the Committee is concerned, because it simplifies the consideration of drug advertisements. He said that the Committee had thought, perhaps, it might work out a more satisfactory scheme, because there appeared to be some drugs, although not submitted to the Council, whose efficacy had long since been proved and recognized and which would not be objectionable for advertising in the ANNALS. However, he

said that the Council has done a magnificent piece of work and that if the College adheres to its previous rule, the Committee will not have to exercise its judgment to any great extent and its work will be simple.)

DR. HUTCHESON: I withdraw my second to the motion.

DR. GRIFFITH: I withdraw my original motion. I move that the report of the Committee be received and filed.

(The motion was seconded from the floor.)

DR. PIERSOL: The adoption of this motion would make our report merely a matter of record, and would omit any action on the recommendation.

PRESIDENT PAULLIN: Mr. Loveland, may we hear from you?

MR. LOVELAND: I would like to say, first, that as a lay Executive Secretary of a society, I am not one of those to whom Dr. Irons referred. It would appear from occasional observations that the journals published by the American Medical Association are the only ones left in this Country that have adhered strictly to the "Council accepted" pharmaceuticals for advertising. I think our Committee was activated in its recommendation by the thought that there are many drugs whose efficacy has long since been proved and recognized, but which as yet have never been submitted to the Council. At no time has our Committee had other than the desire to make the advertising in the ANNALS of the highest possible grade. We refused to accept advertisements of products that are irrelevant to the practice of Internal Medicine, or its related specialties. Many advertisements accepted by the American Medical Association journals are refused by the ANNALS; for instance, we refuse advertisements of cigarettes, pineapple juice, coca-cola, and a whole host of other articles that are advertised in the Journal of the American Medical Association and several of its specialty journals. I believe that all of us will agree that there is no other medical journal whose advertising is conducted on so high a scale as that in the ANNALS. I do happen to know, by personal observations, that many of the State medical journals are now carrying advertising of pharmaceuticals not yet accepted by the Council; there has been a noticeable increase in these advertisements, some of which are of recognized products, and others of which are of products relatively unknown.

. . . . . .

(The motion was put to vote and unanimously carried, which, in effect, made no change in the present policy of the College to accept only "Council approved" drugs for advertising in the ANNALS.)

PRESIDENT PAULLIN: May we have the report of the Committee on Educational Policy, Dr. Ernest E. Irons, Chairman?

DR. IRONS: Mr. Chairman, that Committee met yesterday with Dr. Charles H. Cocke and Brigadier General Hugh J. Morgan present, with Commander Edward L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, in attendance. I was unable to be present, and I will ask General Morgan to report.

GENERAL MORGAN: Commander Bortz presided at the meeting, and I will ask him to make the report.

COMMANDER EDWARD L. BORTZ: Mr. Chairman and members of the Board, our deliberations yesterday were essentially those of review of our experiences with the Postgraduate Courses that were given by the College during the past year. Our program was divided into two semesters, the first one in the winter and spring of 1943 and the second one in the autumn of 1943. The list of courses and the attendance were as follows:

1943 Schedule of Courses:

A. First Semester:

(1) Internal Medicine—University of Minnesota Medical School, Minneapolis, January 25–30, 1943.

(2) Internal Medicine—The Mayo Foundation, Rochester, February 1–6, 1943.
(3) Internal Medicine—Boston University School of Medicine, Boston, April 5–10, 1943.

B. Second Semester:
(1) Endocrinology—University of Illinois College of Medicine and Presbyterian Hospital, Chicago, October 11–16, 1943.
(2) Allergy—Roosevelt Hospital, New York City, October 25–30, 1943.
(3) Special Medicine—Philadelphia Institutions, November 8–19, 1943.

C. Attendance:

Course No.	Civilians	Service Men	Total	Fellows	Associates	Non-Members
1-A	68	9	77	32	17	28
2-A	49	9	58	32	16	10
3-A	51	24	75	33	19	23
1-B	67	11	78	39	20	19
2-B	23	10	33	10	6	17
3-B	68	18	86	41	35	10
	326	81	407	187	113	107

It is estimated that the net cost of these courses for 1943, over and above tuition fees which are collected and paid to the directors of institutions, will be approximately $600.00.

Yesterday the Committee weighed the problem of admitting non-members to the courses. The majority of non-members are Medical Officers in the Armed Forces, but not entirely. Some are aspiring young physicians who hope to qualify for membership in the College and certification in the American Board of Internal Medicine. Before a non-member is accepted, he must be recommended by a Fellow of the College, or by the College Governor of his district. We feel that if a hard and fast rule were drawn, excluding all civilian non-members, it would work a hardship on young men who are serious minded and interested in furthering their understanding of medical problems today and who are looking forward to Fellowship in the College. We must record that pressure for admission to these courses by non-members is often great, but in all instances preference is given to members of the College. Practically every course the College has offered this year, with the exception of the course in Allergy, has been greatly oversubscribed, and it has been difficult to keep the number of attendants within bounds. Our Committee is convinced that in order to utilize to the utmost the opportunities of learning more about modern medical problems today, it is essential to keep these groups reasonably limited in size. A smaller group, naturally, can obtain better instruction and participate more in the deliberations than a large group. In the Committee's opinion, didactic lectures are the least effective and dullest form of instruction. We endeavor to have pathological conferences, roundtable discussions and study groups, in which the teacher is the preceptor, and the students can come close to the master.

The courses continue to be increasingly popular. It was a year ago that we expressed to the Board some misgivings about the possibility of the courses not being so well attended, because of the War—a large number of those in the age group that ordinarily would take the courses is in military service. It was, therefore, an encouraging surprise to find such a great demand for admission to the courses this year. We were not able to accommodate all of the applicants who desired to take the courses. For the Philadelphia course in "Special Medicine," the Executive Secretary turned down some 25 or 30 candidates. The courses have been pre-eminently successful

from the standpoint of numbers, from the standpoint of interest on the part of the faculties, from the standpoint of unqualified support by the institutions, medical schools and teaching hospitals, and from every other angle.

In the light of this experience this year, what is your pleasure for next year? The Committee desires to be instructed as to what the Regents would recommend for 1944. You know the tremendous strain and load that teachers are carrying. It is almost to the breaking point, and yet the men will see the value of these courses and will make their time and abilities available for teaching. I have had close contacts with many of the teachers in these courses, and they have said that never before have they had a more serious minded type of individual and a more stimulating group than that sent by the American College of Physicians. They enjoy having our groups and they feel also that it is rather an official recognition of their institutions. It is a common experience for the deans and directors of these courses to write in and ask when we want the courses repeated; we have invitations from a number of our great medical institutions to put these courses on again.

DR. CHARLES F. TENNEY: According to the report from Dr. Cooke on his course in "Allergy," it appears that a fairly high per cent of the registrants were not members of the College. These courses are organized for the College and for its members; if we are not careful, other men are going to take advantage of them—men who have no connections with our College, and for the price paid they are getting a postgraduate course much too reasonable. For the duration, I think many of the men coming from the Service should have all of this courtesy extended to them, but in the future, I think we must watch that angle particularly.

MR. LOVELAND: Mr. President, I am quite in agreement with Dr. Tenney, but in extenuation of the report on Dr. Cooke's course, we should say that Dr. Cooke was desirous of having a larger group than was represented in the applications by members of the College. His was the only course in which there was a smaller number of members registered than the minimum required. It was with his approval, in this particular instance, that the additional non-members were admitted.

Another thing that is apropos of Dr. Tenney's comments; some institutions have been giving postgraduate courses similar in length to ours and charging a fee of from $125.00 to $150.00, whereas our charge is only from $20.00 to $40.00. Those institutions at the beginning were concerned about participating in our program, because they felt we were, in effect, "underselling them." When we assured them that our program was for members of the American College of Physicians and that we would ourselves underwrite the expenses of the course, take care of registration, promotion, printing, etc., and they would have nothing to do except furnish the facilities, they were favorably impressed and readily agreed to coöperate.

PRESIDENT PAULLIN: You have heard the report of the Committee on Educational Policy. What is your pleasure?

(It was moved by Dr. J. Morrison Hutcheson, and seconded by Dr. A. C. Griffith, that the report be accepted, and that the courses be continued and extended, if in the judgment of the Committee this seems advisable. The motion was put and unanimously carried, and so ordered by the President.)

GENERAL MORGAN: Mr. President, I would like also to move that this Board of Regents, through the President, communicate with the Surgeon General of the U. S. Navy, first, stating that Commander Bortz has done an outstanding job for this College and for postgraduate training, not only of civilian physicians, but also of men in the services, during the past year, and then thanking the Surgeon General for allowing him the time from his regular assignments and commitments with the Navy for this work, and expressing the hope that it will be possible for the Surgeon General to allow him to continue to do this work, because of its great importance in the College.

(The motion was seconded by Dr. Ernest E. Irons. There was no discussion. It was put to vote and unanimously carried, and so ordered by the President.)

PRESIDENT PAULLIN: May we have the report of the Committee on Fellowships and Awards by Dr. Reginald Fitz, Acting Chairman?

DR. REGINALD FITZ: The Committee would respectfully remind the Board of Regents that a resolution was adopted by this Board, December 13, 1942, discontinuing the awarding of further Research Fellowships and of the Phillips Memorial Medal until the end of the War.

Our report, therefore, is concerned only with the completion of the last fellowships authorized by the Board of Regents.

On December 14, 1941, the following Research Fellowships were awarded, in the amount of $1,800.00 each:

(1) Dr. James Hopper, Jr., to work under Dr. John P. Peters in the Department of Internal Medicine, Yale University School of Medicine. Dr. Hopper began his fellowship on September 1, 1942, and completed said fellowship on August 31, 1943, and has submitted a detailed report of the work accomplished and of plans for publication of the results;

(2) Dr. Carl G. Heller to work under Dr. Gordon B. Myers at Wayne University College of Medicine, Detroit. Dr. Heller began his work on July 1, 1942, and completed it on June 30, 1943. Dr. Heller, under date of November 12, 1943, submitted a full report of his work and manuscripts of several of the studies that have been completed;

(3) Dr. Charles P. Emerson, Jr., for work under Dr. William B. Castle, Dr. George R. Minot and Dr. Thomas H. Ham at the Thorndike Memorial Laboratory of Boston City Hospital. Dr. Emerson was unable to accept this fellowship, due to summons to active military duty, but the Board of Regents later ruled that he may file application to resume the fellowship following his discharge from Service, such application to receive special consideration;

(4) Dr. Joseph L. Lilienthal, Jr., to work under Dr. Harvey at Vanderbilt University. Dr. Lilienthal was called to active military service, and was unable to accept his award.

(It was moved by Dr. A. C. Griffith, seconded by Dr. Charles F. Tenney, and unanimously carried, that the report be accepted.)

PRESIDENT PAULLIN: The next will be a report from the Committee on Public Relations by Dr. David P. Barr, Acting Chairman.

DR. DAVID P. BARR: Dr. Griffith and I were the only members of the Committee present. At a meeting yesterday several documents were presented for consideration.

Dr. Arthur C. Bachus, Ripon, Wis., Associate 3–26–39, resigned because he is no longer a specialist in tuberculosis and has entered general practice. He feared he might be called upon to do some minor surgery and obstetrics, and, therefore, thought his usefulness in the College had ended. That brought up a question as to whether the rule now on the books of the College should be enforced during the period of the War. It seemed to the Committee that if one were to apply that rule rigidly we might have to ask the resignation of twenty-five per cent of our members. Outside of the great centers, we recommend the rule be not rigidly enforced during the period of the War.

DR. PEPPER: I second the motion.

DR. PIERSOL: Would that apply to candidates for Fellowship and Associateship, or does it apply only to those already members of the College? There probably is no rule that prevents a member from lancing an abscess, or reducing a fracture occasionally, but on the other hand when candidates come up for election the Committee has been in the habit of assuring themselves that such candidates are internists.

DR. BARR: This case is of an Associate who felt he could not become a Fellow because of his returning to general practice. The recommendation of the Committee would apply to all such cases.

DR. WILLIAM B. BREED: Mr. Chairman, I would suggest that we not go formally on record, because if we do so, it will more or less set a precedent. Can we not better do this informally?

DR. BARR: The Committee feels that the action, if any is taken, should be for Mr. Loveland's instruction, and for the instruction of the Committee on Credentials, rather than any abrogation of the rule.

DR. GRIFFITH: Mr. Chairman, we must consider that there are many of these cases in small communities, where there are Fellows or Associates of the College. With the scarcity of doctors in communities like that, it seems to me that we must consider whether we should adhere to this fast rule of ours, or let the doctor do what he possibly can. The case in point is of a man in a little town of Wisconsin, where there must be only a few doctors.

DR. BREED: Mr. Chairman, I should regret very much to have to go on record that instructions be given, or suggested, to the Committee on Credentials; we are having a difficult enough time as it is. If we have that on record as a direction to the Committee, it will necessarily lower our standards.

GENERAL MORGAN: It seems to me that the very fact this man feels this situation so keenly as to raise spontaneously the question, would make him a very desirable person to retain in the membership of the College, under existing circumstances, and I believe Dr. Breed's suggestion that we handle each case as it comes up, without taking formal action of creating a new regulation, would be a wise way to handle it.

DR. BARR: I think the Committee was somewhat influenced by the letter—a very good letter—which the Executive Secretary wrote, saying in part, "I get the impression that you are entering into the general practice of medicine at Ripon and that you will no longer restrict your work to Internal Medicine and Tuberculosis. If by any chance you are going to restrict your work wholly to Internal Medicine and will not be doing any obstetrics or surgery, major or minor, you may continue your Associateship in the College with the privilege of qualifying for Fellowship. . . ."

PRESIDENT PAULLIN: Dr. Barr, is it your belief that this Associate's resignation should be accepted?

DR. BARR: Yes.

MR. LOVELAND: The Committee on Credentials has raised this question primarily because at their recent meetings, both yesterday and last spring, a number of candidates were deferred until they shall have either reduced, or, in some instances, discontinued obstetrics. If I may speak for Dr. Piersol, the Committee has taken the attitude in the past and up to the present that a different standard shall be applied to the candidate in the small community from that to the candidate in the large center. Candidates from large centers shall restrict their work wholly to Internal Medicine and its allied specialties. The Committee recommended for election yesterday one candidate from a small community, who said he had done twelve obstetrical cases in a year; the Committee felt that in such a community, and especially during the War, such an amount of obstetrics is not particularly objectionable. On the other hand, the Committee rejected two or three candidates whose records show that they were doing from fifty to seventy obstetrical cases a year. At the last meeting of this Board it was pointed out that many of our members will have to do more general practice, and occasionally some obstetrics, during the War, and that the College should not interfere or expect such members to do otherwise, but that they have some obligation to assist during the War in whatever way they can.

DR. COCKE: Mr. Chairman, in extension of Mr. Loveland's remarks, I wish to state that the Credentials Committee has shown more leniency towards candidates

from smaller communities than to those from larger centers. We take that attitude for the duration only, and it is not presumed to be a continuing policy after the War.

(There was no further discussion on the question. The motion was put and unanimously carried, providing for the acceptance of the resignation of Dr. Bachus.)

PRESIDENT PAULLIN: Dr. Barr, will you proceed?

DR. BARR: There are no applications for remission of dues, because of illness or other reasons. Many members of the College on active military duty have expressed their deep appreciation of the waiver of dues for the duration of the War. A few have insisted on paying their dues. A few have said that they felt it would have been entirely adequate had the Board of Regents merely reduced the dues to $10.00 per annum. This matter is not up for discussion at this time, because the Regents took definite action authorizing all members on active duty to be notified that their dues would be cancelled for the duration of the War, and if they desire to obtain the ANNALS OF INTERNAL MEDICINE, the journal will be furnished to them at the reduced price of $6.00 per annum, instead of the usual rate of $7.00.

The Committee reviewed a communication from Dr. George McLean, F.A.C.P., objecting to expressions regarding socialized medicine, expressed by one of the speakers at the Washington, D. C., Regional Meeting of the College in April. The Committee considered this communication and felt that the College, not being a political body, should take no action.

(Dr. Breed seconded the motion; it was put to a vote and unanimously carried.)

DR. BARR: The Committee considered a communication from Dr. Louis J. Bailey, F.A.C.P., of Detroit, requesting aid in improving the organization of the medical section and its conduct at a local hospital. In a masterly letter from our Executive Secretary, he was referred to the Council on Medical Education and Hospitals of the American Medical Association and to the American College of Surgeons. The letter was referred to the Committee, however, with a note mildly deploring the fact that the College has no instructions for such services. It was the Committee's feeling that it is not our function to attempt duplication of work already done by the American Medical Association and the American College of Surgeons.

(On motion by Dr. Breed, seconded by Dr. T. Homer Coffen, and regularly carried, the action of the Committee was approved.)

DR. BARR: The Committee also received a letter from Dr. Stanley Reimann, F.A.C.P., deploring the fact that our secondary schools teach little or no biology and substitute social studies in its place. He requested the Board of Regents to sign a petition recommending that the secondary schools teach more biology and less social studies; also that we specify how much biology shall be taught in the secondary schools of the Country. The Committee felt that while it might be that biology is insufficiently taught in the schools, it would be unwise for the College to condemn social studies or to specify hours for biology, and the Committee recommends no action.

(On motion by Dr. J. Morrison Hutcheson, seconded by Dr. Walter W. Palmer, and unanimously carried, the recommendation by the Committee in regard to Dr. Reimann's resolutions was approved.)

(On motion by Dr. T. Homer Coffen, seconded by Dr. William D. Stroud, and unanimously carried, the report of the Committee on Public Relations was accepted as a whole.)

LUNCHEON RECESS—12:30 p.m. to 1:00 p.m.

PRESIDENT PAULLIN: The meeting will again come to order. We shall have the report of the American Board of Internal Medicine, Dr. Ernest E. Irons, Chairman.

DR. IRONS: Mr. President; first, I want to pay tribute to the members of the Board who have worked hard and long, and who have the prospect of harder and

longer service by reason of increasing number of candidates. In February, 1943, our examinations were held in seventeen civilian cities and in fifty-seven Army and Navy stations. Examinations were also given in Army and Navy stations abroad—in Australia, in the Middle East, in Hawaii, in New Guinea and in North Africa. 179 candidates were examined. There were scheduled for examination on October 19, 1943, 325 in civilian cities, and 87 in military stations. Of the total of 412, 394 took the examination.

Dr. William Middleton has done a grand job in England, and has four General Hospitals at which 33 candidates were examined in October. Altogether examinations were held in 66 Station and General Hospitals in this Country, in 20 stations overseas and in 14 civilian centers in this Country.

There have been certified to date a total of 1,877 without examination. That number is not increasing to any extent. Last year there were only 8, the Board attempting to rectify some earlier oversights.

There have been certified by examination 1,386, and of these 389 were during 1943. In addition, there is a considerable number who has passed the written examination, but has not taken the oral examination, because they are with the Armed Forces. The Board takes the position that unless an oral examination can be directly supervised by a member of the Board, there is nothing to be gained by conducting them outside of this Country.

Financially we are continuing to increase our reserve. We have reduced the examination fee from $50.00 to $40.00. Our cash resources are $46,000.00. We still have to solve the problem of whether to reduce the fee further from $40.00. The Board has endeavored to maintain standards at a constant level. About 25 per cent of those who take the written examination fail; 15 per cent to 20 per cent of those who, having passed the written, take the oral examination, fail. The oral examination can be repeated after one year, and then after another year, if necessary. The written examination may not be repeated in less than two years. We have had wonderful coöperation from the Surgeons General and their offices. (Dr. Irons then read a letter from a Colonel commanding one of the Station Hospitals, expressing appreciation to the Board for conducting its examinations at Service centers, and expressing the desire of his Station Hospital to coöperate in all possible ways in the future.)

This is the representative spirit that we have met all through the Service.

(Dr. J. Morrison Hutcheson moved the acceptance of the report; Dr. T. Homer Coffen seconded the motion, and it was unanimously carried.)

PRESIDENT PAULLIN: Next is the report of the War-Time Graduate Medical Meetings by Commander Edward L. Bortz, Chairman.

COMMANDER BORTZ: Mr. Chairman and gentlemen, this is a progress report of what has happened since the last report to your Board. Here's a map showing the Country divided into twenty-four different zones. We have a committee in each of these zones of three men, one an appointee representing our College, one representing the American Medical Association and another representing the American College of Surgeons. We do not have a full complement, because there has been some difficulty in Regions No. 21 and No. 22 in obtaining the proper spark plugs to act as chairmen, but we have been assured of a remedy to this condition soon.

Briefly, this is an endeavor to conduct a teaching program in medicine of the highest quality in the Service hospitals, especially those away from the metropolitan teaching centers, though not exclusively so. We have thirty-one consultants, each man a recognized specialist in his particular field. Each of these consultants has organized a group of equally qualified men to act as a national faculty. Many suggestions have reached our Central Office about the exclusion or lack of recognition of a number of top-flight men who have not been placed on the national faculties. We believe this a very wholesome sign. Teachers and Deans of medical schools feel

it is a recognition of their services and interest in the war effort for their men to be selected by our consultants for the faculties. We have a national faculty in each of the twenty-eight special fields. In addition, our committees get some teachers from their own particular localities.

In coöperation with the Commanding Officers of the various Station Hospitals, plans of instruction are organized on a weekly or monthly, or even single lecture basis. There is every different type and variety of instruction carried on. We do not encourage straight out and out lectures, because we feel that is a relatively ineffective way of teaching; we have urged that men going into the Service hospitals, spend one, two or more days with the staffs and conduct teaching ward rounds, or participate in clinical-pathological demonstrations, have small study groups, etc.

Our program has gone over surprisingly well. We have received utmost coöperation on the part of about 90 per cent of the Commanding Officers of the various hospitals. We have had particularly fine coöperation on the part of the Surgeon General of the Army, who has been much interested; the men in his office have at all times been most coöperative.

A directive was sent out from the Surgeon General's Office to the Commanding Officers of the various larger Service hospitals, suggesting the wisdom to contact the local chairman for this movement and to arrange for courses of instruction at their hospitals. Thus far, least progress has been made in Southern California, where the Commanding Officers apparently feel there is not anything of particular interest in this program at present. We take the attitude that if they want to participate and to have instruction carried on, we are willing to do it and to put on a program that will be effective and stimulating.

To be sure, this is not fundamentally a great program in graduate medical education, but it is a program that fulfills a real purpose in this time of War. It is stimulating not only to the doctors of the Service hospitals, but to the teachers themselves. It is one move in the right direction; a sort of stop-gap, where the educational link is weakest.

The ideal program, as I see it, and the most stimulating, is in those camps where we already have one or more men who are professional teachers in medicine. We combine their interest and participation with that of our civilian teachers, and that produces a team that is most stimulating to the men in the Service hospitals. . . .

We have sent some teachers into Canada on three or four occasions. (Dr. Bortz proceeded to explain his map; yellow tacks indicated scheduled meetings yet to be held; green tacks, meetings that had already been held. He said that approximately two hundred meetings have already been held, or are scheduled for the near future. He further presented to each member of the Board a brochure of the activities and programs of the Committee, and referred particularly to a model organization in the District of Columbia region, Zone No. 5, by Dr. James Alexander Lyon, Chairman of the Zone.)

The American Medical Association contributed $10,000.00, the American College of Physicians, $5,000.00, and the American College of Surgeons, $5,000.00. At the present time approximately half of these funds have been expended. A report from the Treasurer, Dr. William B. Breed, will be forthcoming later in this meeting. The program is expanding; there is a very wholesome interest on the part of every person. The program is going over in a fashion out of all proportion to what we originally hoped for. Dr. Paullin and Dr. Irons have been two of the moving powers behind the program, and to them real credit is due. . . . I have two office girls who have been working day and night on the project. . . . We in the Central Office have endeavored to be as strict about the expenditures of funds as possible. Three of the Foundations have signified an interest in participating in this program from a financial point of view. President Paullin feels that it is a very wholesome thing for American medicine to underwrite this movement; I think in the future we shall have to ask you

for an additional appropriation, but if there should come a time when you feel we are becoming a little too expensive, it might be possible to have other special societies to participate in financing the program. Some of them already have suggested that we make it possible for them to participate. Our answer was that the program was started under the aegis of these national organizations in American medicine, and thus far they have been willing to bear the weight of expense. . . . Are there any questions?

GENERAL MORGAN: Have you received any reports from the Army, from the personnel visited by this type of instruction? Have you received any suggestions that would lead you to a change of policy or a change of directive for the faculties that give the instruction at the hospitals? I think this type of activity really functions best the closer, the more intimately, the faculty that is visiting a given hospital can relate itself to the functions of that hospital. For example, I think that the man in medicine will accomplish a great deal more by ward teaching and ward rounds than by prearranged lectures. The men in the Army hospitals have perfectly definite jobs and problems with patients. If these specialists go out to these hospitals and simply make their patients the problems and show these men how to handle the cases, that is the ideal thing.

COMMANDER BORTZ: We have the combination. If we have a top-flight man in medicine in a Service Hospital we put one of our teachers with him, and together they put on a clinic or a teaching ward round. We have had hosts of comments from Commanding Officers and from Chiefs of Medicine, Chiefs of Surgery, and so on. (For illustration, Commander Bortz read a letter of appreciation and commendation from the Commanding Officer at the Woodrow Wilson General Hospital, Staunton, Va.) We have the comments from the Commanding Officers and the Chiefs of Medicine, various staff members and also from teachers, because these teachers learn a lot from the Service Hospitals and can utilize that information in their own courses.

DR. WILLIAM D. STROUD: From my experience, I think that the combination of ward rounds and a lecture in which all the officers are allowed an hour and in which they can ask questions is the best method of doing this. If the instruction is entirely confined to ward rounds many of the men are on duty and cannot attend.

(The President relinquished the Chair temporarily to Dr. Charles H. Cocke, First Vice President.)

CHAIRMAN COCKE: May we have the report of the Treasurer of the War-Time Graduate Medical Meetings, Dr. William B. Breed.

DR. BREED: Mr. Chairman, in the hands of the Finance Committee of the College, the following audited financial report has been placed:

COMMITTEE FOR WAR-TIME GRADUATE MEDICAL MEETINGS
CONDENSED STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS
for the three months ended May 31, 1943
and for the five months ended October 31, 1943

	Three Months Ended May 31, 1943	Five Months Ended October 31, 1943	Eight Months Ended October 31, 1943
Receipts:			
American College of Physicians	$ 5,000.00	$	$ 5,000.00
American College of Surgeons	5,000.00		5,000.00
American Medical Association	10,000.00		10,000.00
Total Receipts	$20,000.00		$20,000.00
Cash in Bank and on Hand at beginning of Period		$18,379.53	
Total	$20,000.00	$18,379.53	$20,000.00

Disbursements:			
Salaries	$ 511.34	$ 1,067.07	$ 1,578.41
Equipment	184.20	16.00	200.00
Communications	78.09	352.57	430.66
Office Supplies	151.93	127.99	279.92
Printing	119.60	204.75	324.35
Travel Committee	315.29	187.74	503.03
Travel Instructors	260.02	1,638.32	1,898.34
Miscellaneous		41.35	41.35
Total Disbursements	$ 1,620.47	$ 3,635.79	$ 5,256.26
Cash in Bank—May 31 and October 31, 1943	$18,354.51	$14,736.53	$14,736.53
Cash on Hand—May 31 and October 31, 1943	25.02	7.21	7.21
TOTAL CASH IN BANK AND ON HAND—May 31 and October 31, 1943	$18,379.53	$14,743.74	$14,743.74

You will be interested in some of the highlights in our expenditures. To illustrate the acceleration of this program: in 8½ months the Committee has spent $9,864.00; in the first 5 months it spent $3,635.00; in the first 15 days of November it spent $4,608.00. If this goes on at the present rate our funds will be exhausted very soon. It is almost a critical situation, for you can readily see it will not take very long to deplete the remaining cash on hand.

The total amount paid to instructors was $5,000.00, approximately. Of that, $4,500.00 was spent on travel, and $500.00 for honoraria. It has been decided that a man who spends five days away from home is entitled to $25.00 a day, but any shorter travel is not paid for, that is, in addition to his traveling expenses. The average travel expense has been $15.00; the highest honorarium, $175.00.

With your permission I should like to talk a little bit about the New England setup. Fortunately the First Service Command and the First Naval District coincide almost exactly with the two regions of the national postgraduate committee. All the postgraduate teaching facilities in this area have been incorporated under a New England War-Time Graduate Committee. On that Committee the regional chairmen sit, the representatives from the medical societies of all the States concerned and the Medical Officers of the First Service Command and the First Naval District. A program was set up and submitted to both the Services; not only were these programs accepted, but both the Army and Navy and the Chief Medical Officers requested and sent out directives to the local Medical Officers in these installations providing that twice a month there should be a team come to each one of the eighteen installations in New England. By this procedure we are not relying upon the varying temperaments of local installation medical officers.

We have twenty-one teams; I won't discuss them all, but one team consists of a specialist in stomach, biliary tract, intestinal disorders, an internist, a surgeon and a roentgenologist. These specialists cover the various titles, or fields, set up in our program as a whole—twenty-one in all.

There are eighteen installations extending from Bangor, Maine, down into New Haven and Rhode Island. The scheme is to have a team spend only one day, a half day on ward rounds, perhaps during the afternoon, and in the evening panel discussions concerning the case presented at ward rounds. I have discussed our plan not to compete with the plans in the District of Columbia or elsewhere, but to show that with varying conditions and setups we put in effect different schemes which illustrates the elasticity of the system.

CHAIRMAN COCKE: May I ask, Dr. Breed, if your activities go on at this accelerated rate what limits do you suppose you are going to put upon it?

DR. BREED: Well, there are a great many programs now in process; I don't expect it to slow up. If we don't have money, we shall have to close up shop.

DR. TENNEY: Did not Commander Bortz say that there are some funds available through other sources?

COMMANDER BORTZ: I said there had been one or two other special societies that suggested that they would like to participate in the plan. Whether or not the Board would consider it advisable to entertain the idea of funds from one of the Foundations, I suppose the Board will have to decide.

(President Paullin resumed the Chair.)

PRESIDENT PAULLIN: As far as the American Medical Association is concerned, they would not entertain the idea of a Foundation coming in and taking over this project. They think it is entirely too valuable an activity and that it is an obligation of American medicine. They feel that the group that is now doing this is the logical one to take care of it. Only yesterday the Finance Committee of the Board of Trustees voted us $20,000.00 more and the American College of Physicians voted us $5,000.00 more.

BRIGADIER JONATHAN C. MEAKINS: I move that the American College of Physicians gives $5,000.00 additional.

DR. GRIFFITH: I second that motion.

DR. PEPPER: Such provision is included in the budget to be presented by the Finance Committee.

PRESIDENT PAULLIN: Insofar as finances are concerned, I haven't the slightest doubt in the world that the groups that are primarily interested in this work, seeing what has been accomplished, agree that it is one of the finest jobs that has ever been put over.

DR. IRONS: Mr. Chairman, I think that if any dire necessity arose, it would be quite acceptable to take some Foundation money, providing there are no strings to it and that the present administration handles it.

. . . . . .

DR. BREED: I would like to call your attention to the fact that if this program doesn't accelerate any faster in two more months the new $10,000.00 or $20,000.00 will be gone.

COMMANDER BORTZ: I would like to ask General Morgan if there is any Officer in the Army who could work as a coördinator with the Committee and who could help us to iron out a number of perplexing problems that arise from time to time?

DR. IRONS: I suggest General Morgan himself.

GENERAL MORGAN: I don't know. Actually, as the Army is administered through the Service Commands, the Service Command Surgeon is, as you know, the fellow that I would think to be the top man locally. Anything that the Surgeon General might do would be purely in terms of expressing interest or acting as an adviser to the Service Command Surgeon. I would be glad to do what I can in connection with any problem that may come up. If I can't help, I might go to somebody in the Office who could.

COMMANDER BORTZ: One of the most perplexing problems that we have is the question of transportation. Down in New Mexico and Arizona we have had a number of splendid meetings, but the matter of transportation has been difficult, and the men find it necessary, at times, to fly. To fly they need priorities. The question is how to get them.

PRESIDENT PAULLIN: I think that can be worked out later. We have a full program and must proceed. Next is the report of the Committee on Post-War Planning for Medical Service, Dr. Walter W. Palmer, Chairman.

DR. PALMER: The Committee on Post-War Planning was appointed by President Paullin with the approval and authorization of the Executive Committee of the College last February. Dr. Morris Fishbein proposed that such a Committee be appointed to meet with a larger Committee composed of representatives from leading medical organizations in the Country, including the American Medical Association

and the American College of Surgeons to meet at a banquet in New York City on the invitation of The Carlos Finlay Institute. At this banquet were representatives from the leading manufacturers of drugs and medical supplies, as well as from the fields of publicity. The guests were invited to attend "The National Conference on Planning for War and Post-War Medical Services." The speeches made at this banquet are to be published.

On June 5, 1943, the large Committee met in Chicago. Several representatives from the American Medical Association, the American College of Surgeons and this College were present. At this meeting the discussion was largely exploratory. The post-war problems which seemed certain to arise, centered around education, location and distribution of returning younger physicians and public health responsibilities.

On October 15, the large Committee met again in Washington. The account of this meeting was published in the Journal of the American Medical Association, October 30, 1943, page 574. The subjects of the previous meeting were considered. Three sub-committees were appointed:

1. Relocation of Medical Officers Returning from the War. Doctors Gregg (Chairman), Allen and Piersol.
2. Post-War Vocational Training Periods—internships, residencies and training in the specialties.
   Doctors Palmer (Chairman), Collin and Blake.
3. Collection of Information from Physicians in Service as to What is Desired in the way of Education and Position after Leaving the Service.
   Doctors Abell (Chairman), Mason and West.

The medical problems which are bound to arise in the invaded countries were discussed and no action taken.

Because of the importance of the Veterans Bureau Services in many of the post-war medical problems, the Committee voted unanimously to invite the Director of the Veterans Bureau to appoint a representative as a regular member of the Committee.

The first meeting of the Committee of the College met yesterday at 10:15 a.m. Doctors Bortz, Breed, Piersol and Palmer were present. It was the sense of those present that our Committee should not initiate any special plan of the College at the present time, but confine itself to coöperating with the main body. The Committee considered a suggestion made by the Executive Secretary, Mr. Loveland, that a central bureau be established in the College for the purpose of helping members in Service in the problem of relocation after leaving the Army or Navy. Since such a bureau is contemplated on the part of the main Committee, it would seem unwise to duplicate the activity in the College, unless this proved to be a special need.

PRESIDENT PAULLIN: May we have a report from the Chairman of the Board of Governors, Dr. William B. Breed?

DR. BREED: Mr. Chairman, as you know there has been no meeting of the Board of Governors since the Annual Session in St. Paul. I cannot bring you any personal news from the Board as a whole. I can report, however, that in response to a letter a year ago, the Governors have shown a great deal of initiative and interest in arranging Regional Meetings, which you know about and which you have heard discussed here. Recently I sent to all Governors a letter about the question of some sort of an Annual Meeting in 1944. I sent out sixty-two letters and I have received a total of forty-one replies. Of the United States Governors there were six only who voted against any kind of an Annual Meeting, who probably wish to rely primarily upon the Regional Meetings for the duration. Of those who favored some sort of a meeting, six United States Governors thought that we ought to have an orthodox Annual Meeting; twenty-five favored a modified meeting of some sort. This latter group was not specific, but all were certain that a Business Meeting should be held. Now,

that makes thirty-one out of thirty-seven who believe that an Annual Business Meeting at least should be held and six who believe that a regular orthodox meeting should be held.

I heard from three Canadian Governors—one was against any meeting; one was for an orthodox meeting; and one was for a modified meeting.

One of the Surgeons General was in favor of an orthodox meeting.

Of the total of forty-one replies, seven were against any meeting and thirty-four were in favor of some sort of a meeting.

(On motion by Dr. O. H. Perry Pepper, seconded and regularly carried, the report of the Chairman of the Board of Governors was received and filed.)

PRESIDENT PAULLIN: Next is the report of the Treasurer, Dr. William D. Stroud.

DR. WILLIAM D. STROUD: We have placed in your hands the operating statements from January 1, 1943, through October 31, 1943, with estimation for November and December. At the end of the year, the accounts will be audited by a Certified Public Accountant, and official copies mailed to all members of the Board of Regents.

The invested funds of the College on November 5, 1943, at market value were as follows:

Endowment Fund	$140,443.75
General Fund	112,476.25

or a total of $252,920.00. The average yield on our investments, both Endowment and General Funds, has been 3.76 per cent, amounting to an annual income of $9,512.50. We still feel that the Investment Counsel of Drexel & Company has done a very satisfactory job, and with their advice, we are making an additional investment for the Endowment Fund of approximately $6,000.00, and for the General Fund, approximately $10,000.00; and upon January 1, 1944, shall make further investments from the General Fund of $20,000.00, which will bring the total investment for the Endowment Fund to approximately $146,000.00 and for the General Fund to approximately $142,000.00, or a total investment for the College early in 1944 of $289,000.00, as compared to a year ago of approximately $252,000.00, or an increase of approximately $37,000.00 for this year.

(On motion by Dr. O. H. Perry Pepper, seconded by Dr. A. C. Griffith, and regularly carried, the Treasurer's report was received and filed.)

PRESIDENT PAULLIN: Next is the report of the Committee on Finance, Dr. O. H. Perry Pepper, Chairman.

DR. PEPPER: The Finance Committee met at the College Headquarters on Friday, November 19, 1943. Present were Doctors Stone, Stroud and Pepper. Dr. Bruce was unable to be present.

The Committee took cognizance of the fact that all figures for the year must include estimated income and expenditures for November and December.

The Committee noted with pleasure the marked increase in income, as compared to the estimates of a year ago. The actual income will exceed the estimated income approximately $15,300.00. This figure is made up chiefly from the following items:

Increased income from Investments	$2,500.00
Increased income from Subscriptions to ANNALS	6,000.00
Increased income from Life Membership Fees	7,400.00
Increased Profit on Securities	600.00

Every department of the College operated below budget provision, with the exception of the College Headquarters, which went over by $120.00. This was due to depreciating office furniture and equipment, $800.00, which was not budgeted. Consequently, the budget actually was not overdrawn. As a whole, the College will have operated below its budget approximately $6,600.00.

The Committee has reviewed the budgets for 1944, as prepared by the Executive Secretary. It is to be noted that the only increments are two small increases, totaling $180.00, in salary for the secretaries of the Editor of the ANNALS. These are recommended because of length of service.

The Budgets, as prepared by the Executive Secretary, for 1944 total $77,315.00, which is less than the budgets approved a year ago. In the budgets suggested by the Executive Secretary, the Committee recommends some additions and changes:

(Dr. Pepper discussed the proposed additions and changes, which increased the total budget by $3,900.00, to a grand total of approximately $81,215.00. He pointed out that the total estimated income of the College for 1944 is approximately $93,000.00, and that, therefore, a surplus of about $12,000.00 is anticipated, which he considered safe and satisfactory.)

Mr. President, I, for the Committee on Finance, recommend the approval of the budget as prepared by the Executive Secretary, plus the appropriation of $3,900.00, as detailed in my remarks.

(The motion was seconded by Dr. A. C. Griffith. There was no discussion, and it was unanimously carried and so ordered by the President.)

PRESIDENT PAULLIN: Next on the program is special problems and topics. Dr. T. Homer Coffen has a problem concerning certification.

DR. T. HOMER COFFEN: I have had concern for some time because of questions regarding certification that have been asked me by Fellows who have been accepted by the College for Associateship and for Fellowship, and then because they did not come under the ruling of 1937, or possibly of 1940, now must take the examinations in order to be certified. Sometimes I think this has been a matter of curiosity and other times a little resentment or misunderstanding. On the other hand, I have been surprised at the acceptance of the necessity of being certified for admission to Fellowship by young men, because they are all very anxious to get this examination back of them and be recognized as qualified internists. I raise the question merely because of this curiosity which has been shown, and to me, perhaps, some unfairness. It is embarrassing at times. It is difficult to say whether such and such a person should be certified without examination, and occasionally that has caused some confusion. . . . If I have had such questions and such experiences, I suppose others have also, and possibly I could be enlightened as to how to satisfy these gentlemen. In the case of those who are now in the Service, Fellows who have not been certified, we might think of some way of their being excused from examinations.

PRESIDENT PAULLIN: Does anyone wish to discuss this question? Dr. Irons is out. Would you like to wait until he returns, Dr. Coffen?

DR. COFFEN: Yes.

PRESIDENT PAULLIN: Next for consideration is the question of whether we shall have an Annual Session in 1944. You have heard the remarks presented by Dr. Breed concerning the feeling of the Board of Governors. The American Medical Association has definitely determined to hold a meeting, June 12–16, 1944, in Chicago, and other medical organizations—the Southern Medical Association has held its meeting in Cincinnati this week, at which they had a large attendance; the Association of Military Surgeons had their meeting in Philadelphia about a month ago, with a large attendance. So the question comes up as to whether the College should abandon its meeting and go on in status quo with Regional Meetings, or whether we should resume our Annual Session. The Chair would like to have your reaction to this question. So far as I personally am concerned, I should be delighted to have a meeting.

DR. GRIFFITH: We are all hoping that some favorable outcome from the War will be shortly forthcoming and that will make travel a bit better. As it is now, I think the great problem of all people is to get from one place to another by train or plane.

If the meeting could be held in a central location, I think it would be less difficult to reach than if it were held in the East. I have heard some reports that train travel is to be rationed. What effect would that have on medical meetings? I am much in favor of having an Annual Session, if we can possibly do it. We had in Kansas City a meeting of the Southwest Clinical Society, which includes many States around that part of the Country. We had the largest attendance we have ever had at any of those meetings, and they have been going on for fifteen or so years. That is quite definite evidence of the fact that doctors are anxious to get away and get to some of the meetings for a rest, if nothing else.

DR. BREED: Mr. Chairman, has there been any concrete suggestion as to how our meeting could be modified, if it were decided not to have the orthodox regular meeting with Convocation, and so forth?

PRESIDENT PAULLIN: I cannot answer that. Can you, Mr. Loveland?

MR. LOVELAND: No. The various recommendations that have come into my office have been somewhat obscure and not clear in regard to exactly what was meant. Visitors to the College Office and correspondents from among our members have been in favor of some sort of a modified meeting, which could provide, under the By-Laws, for an Annual Business Meeting, the election of Officers, Regents and Governors. I think the consensus among those to whom I have talked is that to resume a full-fledged Annual Session now would be like "holding your fire so long and still shooting too soon." We have emphasized in our literature that we will not hold a Convocation until the end of the War, and then it shall be a great Victory Celebration at which we shall induct the several hundred new Fellows elected since the St. Paul Session. We could hold a modified Annual Session without a Convocation, the meeting being called primarily for the purpose of conducting the business of the College, including the election of Officers. It would be possible also to have a limited scientific program, although the program phase has not been discussed.

DR. COFFEN: What would attract members who are not connected with the Board or otherwise connected with the official running of the College, to assure a reasonable representation for the election of new Officers, Regents, etc.?

DR. FITZ: Mr. President, when this letter first came out I was firm in my mind for voting against a meeting; subsequently, I have talked to a great many people and I think it astonishing, first, the success of the postgraduate program, showing how many men want to do something, and, second, the success of the recent Interstate Postgraduate Assembly, which I understand was the largest meeting they have ever had. All over the Country doctors do want to come to meetings. It seems to me that the College really ought to have a meeting to let the men know that the College is still running, and that we should give as good a program as we can. It makes little difference whether or not we hold a Convocation, but I think we ought to have the Presidential Address as usual. Whether we actually induct the new Fellows as we have in the past is a minor issue, but I believe all the men who come would appreciate it very much and would like the opportunity of attending as good a meeting as we can give them.

DR. PEPPER: Remembering the small number of members who attend the Business Meeting even at our biggest meetings, I am wondering if we need a great number of men at the Business Meeting to elect Officers. I never have heard the slate that was presented questioned. Our By-Laws are probably drawn so that a quorum is a percentage of those present. What are the By-Laws?

MR. LOVELAND: A majority.

PRESIDENT PAULLIN: Gentlemen, if a meeting is contemplated, my information is that it would have to be characterized as a meeting to accelerate the War effort. In other words, it would have to be called a War Meeting of the American College of Physicians, a meeting that is planned to accelerate the enlistments of physicians into the Army and Navy, of which there are a very few more to go; a program for the

better education of doctors that are already in the Service, to acquaint them with military problems that are bound to arise. It is only under conditions, such as that, I think, that Mr. Eastman would allow any such meeting to occur. Perhaps there would be some difficulty in promoting such a meeting. If we are convinced of the necessity of it, intervention probably could be made in our behalf with the Office of Defense Transportation, to see that we could get accommodations to meet. Of course, the other problem is where shall we meet and how many days should the program cover. If we are going to have a meeting we ought to decide that now; it will take time to make the necessary preparations.

DR. COCKE: Mr. Chairman, would any instructions of the O.D.T. apply to the recent meetings of the Southern Medical Association and the Interstate Postgraduate Assembly?

PRESIDENT PAULLIN: So far as I know, the question has not been actively raised, but it is always in the offing.

DR. COCKE: I cannot see that the program of the Southern Medical Association was particularly directed to the specific problems of a war meeting.

PRESIDENT PAULLIN: There was a great deal of military medicine; as a matter of fact, they advertised it as a war meeting.

MR. LOVELAND: Mr. President, there is another principle involved. If we have an orthodox Annual Meeting and put the emphasis on that, we shall have to take the emphasis off of our Regional Meetings over the Country. We could still encourage Governors to conduct their individual State meetings, but we could not conduct an Annual Session and twelve or fifteen large Regional Meetings, such as we have done this year. The Regional Meetings have been purely an interim activity and I suppose when we resume our Annual Sessions, we shall reduce our Regional Meeting activity.

DR. PEPPER: Mr. President, may I ask Mr. Loveland a question? If we hold an Annual Meeting, the expenses of which are largely met by our commercial exhibitors, we might not wish to hold a meeting with commercial exhibits during war time or we might not be able to hold a meeting with a real commercial exhibit. That would then make the meeting an expense, which would naturally interest the Finance Committee.

DR. IRONS: Mr. Chairman, the experience I think is that the commercial exhibitors are extremely anxious to get a place to show their goods. You would have no difficulty in getting exhibitors.

DR. GRIFFITH: When we had a meeting in Kansas City, we had just as many commercial exhibits this year as we ever had.

MR. LOVELAND: Those societies that have continued to hold their Annual Sessions throughout the War, with the American Medical Association, the College of Physicians and the College of Surgeons out, have reaped a great harvest from their exhibits. Other opportunities to exhibit being limited, it seems that all the exhibitors have flocked to those meetings.

DR. COCKE: The Regents decided at St. Paul to hold the next meeting of the College in Philadelphia. That has not been rescinded.

PRESIDENT PAULLIN: Gentlemen, what is your pleasure? Will someone make a motion?

DR. FITZ: Mr. President, just for the sake of getting something started I should like to move that the College have an Annual Session in 1944, and that the clinical program be in large part devoted to military medicine, but that due consideration be given to civilian medicine, in accordance with numerous requests from men in uniform, and that we have an Annual Meeting without the ordinary Convocational ceremonies at which new members are inducted, but that the Presidential Address shall be included.

DR. GRIFFITH: I second the motion.

PRESIDENT PAULLIN: You have heard the motion. Is there any discussion?

DR. COCKE: How much of a problem would be presented by the housing situation in the average city? Has that been a feature that has been hard to solve in recent meetings?

DR. BREED: I just read an article to the effect that hotels in New York have restricted accommodations to functions having to do only with furthering the war effort. When we spoke of having a war meeting, I thought that that answered the particular question.

(There were several calls for the question, but when voted upon there was a division—seven votes for the motion, six votes against the motion.)

BRIGADIER MEAKINS: I didn't vote, Mr. Chairman, because this problem revolves around a very important domestic situation in the United States. However, I would be against it.

GENERAL MORGAN: I wonder if we could have further discussions relative to reasons against having a meeting. We have heard very little about that. I think we might very well declare the question still open and that we shall consider it in the light of arguments against the meeting.

PRESIDENT PAULLIN: Dr. Hutcheson, would you like to open the discussion? You voted against it.

DR. HUTCHESON: Since I received your letter sometime ago, I have given the matter some thought. I think it is highly desirable to have a change of Officers, Regents, and so forth.

PRESIDENT PAULLIN: It certainly is.

DR. HUTCHESON: There are many reasons for having a meeting; the reasons against having the meeting include the transportation situation and the pressing demands upon physicians at home. It seems to me that the same reasons exist now and will exist another year that existed last year, when we postponed the Annual Meeting. The transportation situation is the important one. Trains and planes are tremendously crowded, hotel facilities are difficult to secure. There is also the additional consideration of the Regional Meetings, which it seems to me might be seriously interrupted if we hold a General Session.

PRESIDENT PAULLIN: Do you object to any kind of a meeting?

DR. HUTCHESON: I do not see how any intermediate meeting could be effective. I do not think members of the College would travel any distance to a meeting if we did not have a program, but merely a meeting to vote for Officers.

DR. COFFEN: Mr. Chairman, I, too, felt rather opposed to an Annual Session next year, but since there is the possibility of our really doing something in a military way, as well as for our members, I am now in favor of it. Travel from Chicago to the West Coast is most difficult, and I doubt if there would be very heavy attendance from that region, but there would be a number of men who would make the effort.

DR. STROUD: Dr. Hutcheson has expressed my views on the matter. After all, the only reason for having the meeting would be for our College to continue to do the best it can for American medicine. I think we are doing that through these Regional Meetings and the other programs we are advancing. It would be placing an added burden on the transportation of the Country, and I do not believe that American medicine would suffer if we do not have an Annual Session next year.

PRESIDENT PAULLIN: Dr. Piersol, will you express your feeling?

DR. PIERSOL: In addition to the arguments that have been advanced, I, too, feel that these Regional Meetings are serving the purpose; to accelerate them and to increase their number and efficiency is probably doing just as much for our membership and giving them as good an opportunity as an Annual Meeting would. When you consider the attendance at these Regional Meetings in sum total it exceeds that of any Annual Meeting. Our meetings in the past have always been outstanding. It would be almost impossible, in my opinion, certainly very difficult, to offer a clinical session at this time in any medical center that would be comparable to the sort of meetings we have held in the past. We should not put on a meeting which would fall

below our standard. Also, I think it would be difficult to go to any of these cities now and approach the medical schools and teachers, and others, and ask them to get up a program and do the necessary work. It would take a lot of temerity to go to these faculties, many of which are already doing a lot of work, such as going out on these expeditions for the War-Time Graduate Medical Meetings, which is only one of the added loads which they carry, and ask them to take the added burden of organizing a big medical meeting. It is possible, but it certainly would be very difficult, and it seems to me an unjustified burden. I do not think there is any justification for it, not when there is all this teaching going on all over the Country and all the work being done for the Armed Forces. It would be largely a duplication, and its basic motive would be to get together to have a Business Meeting, in order to transact certain things, to elect Officers.

DR. BREED: The impression I received from these letters from the Governors was that they felt a Business Meeting and the election of Officers, Regents and Governors is a very important matter. Is it entirely impossible to accomplish this end by a mail ballot?

PRESIDENT PAULLIN: I think Dr. Pepper can answer the question.

DR. PEPPER: This matter was discussed last year. I take the same position that I took then. I think the mail ballot is probably impossible, under our By-Laws. I see no reason, however, under our By-Laws, why we cannot call an Annual Session without any scientific business; the notice going to the members that an Annual Session is being called, but that due to war conditions, there will be no commercial exhibits, no panels, no scientific program, that the following slate has been prepared by the Nominating Committee as usual, and that any one who wishes to come to the meeting to vote will be welcomed. We will accomplish everything that is desired in the way of business by having a meeting of the Regents and Governors, and we will avoid the danger of having a half-good meeting. We will avoid the criticism that has applied to every meeting that has been held, that they were occupying hotels and train reservations; it seems to me this is the answer. I do not see any objection to it; it is legal; it will accomplish what we want.

PRESIDENT PAULLIN: Dr. Stone?

DR. STONE: I have mixed feelings about this. I might favor the Annual Meeting and yet I see full well the difficulties. The proposal that Dr. Pepper just made strikes me very forcibly. I would favor it over the general meeting, in view of what has been said.

DR. PEPPER: May I say one additional thing? We have been told of a large attendance of the Southern Medical Association and the Southwest Clinical Society. These, in a sense, are Regional Meetings. No one, except the speakers, had to travel the length and width of the Country, or even half of it, to attend those meetings. We are now starting to have a big central meeting somewhere, asking people to come the entire distance. The American Medical Association has already decided to stage such a war meeting. The very same speakers that we would want, the top-notchers from the Army and Navy and the Public Health Service and that sort of thing, will be on their program. Organized medicine is going to have one big meeting. It seems to me that that is enough for the purpose. I think our meeting will be superfluous.

BRIGADIER MEAKINS: Mr. Chairman, to my mind there is somewhat of a paradox in this evangelical zeal at the present moment for attending medical meetings. We all know that the practicing physicians have been reduced in numbers by something like 35, 40 or 45 per cent, but still these men can get away for ten days, or a week. Why is it? I think they want to get away not so much to absorb medical knowledge, but to get away from boredom and their work.

PRESIDENT PAULLIN: Dr. Bortz, what is your reaction?

COMMANDER BORTZ: The meeting of the Association of Military Surgeons here was far and away the most successful meeting they ever held. I rather disagree with

Brigadier Meakins, for I have been to a great many of our Regional Meetings, and a number of other medical meetings, and I have never seen a time when the interest on the part of the doctors was so intense and when they were so eager to keep abreast of the medical times. There are important new developments in medicine taking place today in many fields—the fields of chemotherapy, blood substitutes, etc. There is important new information that the doctors are eager to have. The question of having a scientific program would seem to be duplicated by the number of men who will be on the program of the American Medical Association, if we endeavor to have one. There would be topics on our program that will certainly be the major topics for discussion on the American Medical Association program. I am enthusiastic about our Regional Meetings. They have a definite purpose in the structure of action of the American College of Physicians. I think they should be encouraged from the standpoint of scientific program, and I believe the College should certainly and definitely have a Business Meeting in 1944, and then study the situation further. In that event, we could still consider a scientific program for the following year.

At the present time I believe there would be absolute duplication by our College and the American Medical Association; we would have our meeting in April or May and the American Medical Association will meet in June.

DR. FITZ: Mr. President, we should remember one thing. No matter if the men who talk at both places should be the same, the program is quite different. What members of our College like is to go to the clinics and, above all, to go to the panel discussions. In regard to the Regional Meetings and the war teaching program, men not in uniform are at a disadvantage. A great many civilians would very much like to have a chance to come to a meeting here, to hear discussed from the military points of view some of the things the soldiers are seeing, just as, conversely, men in uniform would be delighted to attend once again a medical clinic given by their former professor. We could do a great deal in building up a spirit in the College, that a great many members would appreciate.

(A motion was made to reconsider the action of the Board of Regents in declaring one vote in favor of the Annual Session. This was seconded and the above discussion has been on the question of reconsideration. There was no further discussion on the motion. The motion was carried unanimously and so ordered by the President.)

DR. PEPPER: Mr. President, I move that the American College of Physicians hold an Annual Session during the year 1944, without a specific scientific program, but with a regular Annual Business Meeting, as provided in the By-Laws, and meetings of the Board of Regents and of the Board of Governors.

(The motion was seconded by Dr. Tenney. There was no further discussion and when put to the vote, it was unanimously carried and so ordered by the President.)

(By common consent the time and place of the meeting was left to President Paullin, Executive Secretary Loveland and Secretary-General Piersol.)

PRESIDENT PAULLIN: Dr. Irons, there was a matter up for discussion by Dr. Coffen concerning certification by the American Board of Internal Medicine. You were not present at the moment, and did not hear it. Won't you and Dr. Coffen talk over this problem and clarify it between yourselves.

DR. PEPPER: Does the holding of a meeting, such as contemplated, involve any expenditure by the College which should be included in our budget for the coming year?

PRESIDENT PAULLIN: Mr. Loveland, can you answer that?

MR. LOVELAND: A question arises in my mind rather forcibly about asking the Governors to come from all parts of the Country to a meeting at their expense, when there is no other reason therefor than their ordinary interest in the College—no scientific program, etc. There is no other particular expense involved unless provision were made for the paying of their travel expenses.

DR. BREED: Mr. Chairman, I think that that is a well taken point. Just looking forward to a meeting of that kind without the surrounding scientific program, I

am wondering how we could really interest the Governors. Certainly I should think they would not be willing to come any great distance at their own expense.

DR. PEPPER: The Secretary has just informed me that a quorum for the Board of Governors for their meeting is fifteen. He reminds us that the By-Laws provide that the Board of Governors shall meet in executive session annually at the time and place of the Annual Meeting of the College.

DR. PIERSOL: Isn't it really an important thing, psychologically, if in no other way, to have a meeting of the Board of Governors? I think one of the advantages of having this Annual Meeting would be not only to facilitate our business, but to let our Governors know that they are a part of our body. They are really a very important body and carry a lot of weight.

PRESIDENT PAULLIN: We must have some sort of an agenda for their meeting, aside from the Annual Business Meeting of the College.

DR. BREED: Mr. President, I think Dr. Pepper's suggestion that the Board of Governors be invited to hold a joint meeting with the Regents at the time of the Annual Session would be in order and quite fitting.

DR. PEPPER: I move that the expenses of the Governors be paid on the same basis as those of the Regents; that they be invited to sit with us in joint session at all of our deliberations.

(The motion was seconded in rapid succession by Doctors Hutcheson, Griffith, Tenney and Breed; there was no discussion. The question was put and the motion unanimously carried and so ordered by the President.)

DR. PEPPER: This will require no action for the budget today, but may be paid out of surplus.

PRESIDENT PAULLIN: Gentlemen, Mr. Loveland has a statement to make.

MR. LOVELAND: I really do not know how to make the statement, but I assure you I have no words to express adequately my appreciation of your recognition of my work and efforts with the subsequent increase in my salary. I am deeply grateful.

PRESIDENT PAULLIN: I assure you, Mr. Loveland, on behalf of the Regents, Governors and all members of the College, that we deeply appreciate your kindness, your thoughtfulness and your wonderful service, which you have given us, and this is just a mere pittance in expressing our thanks to your service.

DR. GRIFFITH: Will there be a meeting of the Nominating Committee?

DR. BREED: Yes, sir. That brings up another point. It probably will be important to have a personal meeting of the Committee for nominations, and I, as Chairman, would recommend such a meeting be obligatory and not have all this business done by mail. That brings up the question as to whether the expenses of the Committee on Nominations shall be paid.

PRESIDENT PAULLIN: Who is on the Committee?

DR. BREED: Doctors Hugh Morgan, Chauncey Dowden, James Churchill and Fred Smith, and myself, as Chairman. It should be a meeting sometime in advance, at least a month or two, and then it must be published a month in advance in the ANNALS.

DR. TENNEY: I move that the travel expenses of the Committee be paid to the place of meeting.

PRESIDENT PAULLIN: Have they done that in times past?

DR. GRIFFITH: No; it has been done by mail.

PRESIDENT PAULLIN: Dr. Breed, you are a good correspondent. See what you can do by mail.

DR. BREED: I surrender.

Adjournment

Attest (Signed) E. R. LOVELAND, *Secretary*